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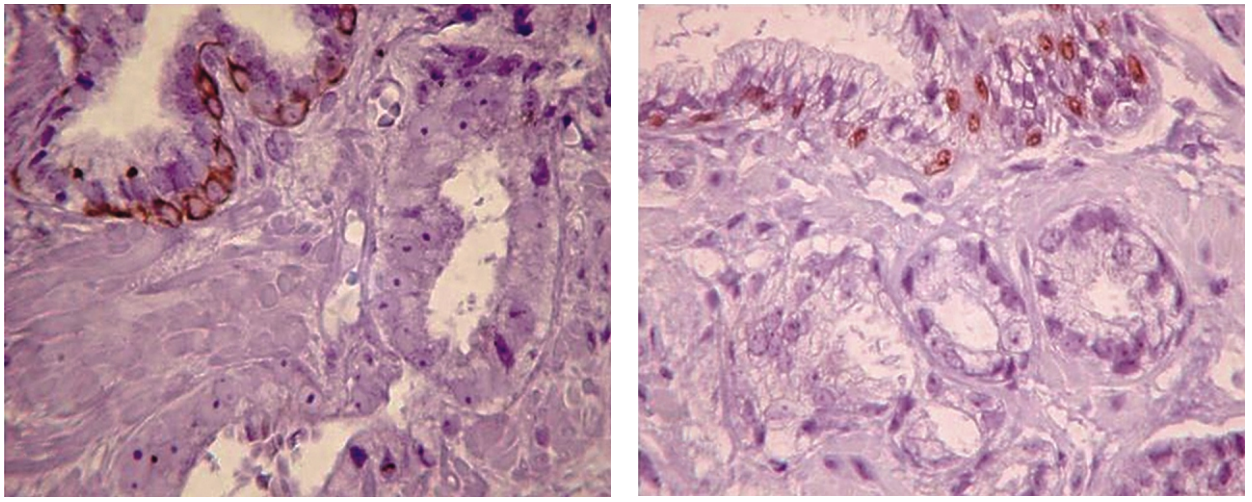

Immunostaining of prostate biopsy demonstrating absence of basal cells characterizing cancer. (Page 583)

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EDITOR'S COMMENT

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Current Contents / Clinical Medicine

With the September-October 2010 issue, it is our great pleasure to announce that the Int Braz J Urol has been covered by Thomson Reuters (ISI) Current Contents / Clinical Medicine since January 2008. The journal has been included in the Science Citation Index Expanded, accessible through the Web of Science. Our official Impact Factor will appear in the 2010 Journal Citation Report (JCR), which will be released in mid-2011. Our current unofficial Impact Factor is 1.2, calculated in the same way that ISI generates its Impact Factors. We are confident that it will be higher in the 2010 JCR.

As you know, the Int Braz J Urol is an open access Urological Journal (www.brazjurol.com.br) that publishes peer-reviewed articles on all aspects of Urology, from prevention, diagnosis and management to molecular biology, pathophysiology, and epidemiology.

Thanks to its high quality peer-reviewed articles and its open access, the published articles are accessed more than 30,000 times each month from our website and additional many times from PubMed Central.

We are most grateful for your continuous support to the Int Braz J Urol and look forward to receiving contributions from you and your team.

The September-October 2010 issue of the International Braz J Urol presents original contributions and editorials from many different countries, such as USA, Germany, France, Brazil, Italy, Thailand, England, India, Portugal, Iran, Israel, Japan, South Africa, Switzerland, Egypt, etc., and as usual, the editor's comment highlights some papers.

Doctor Sexton and colleagues from H. Lee Moffitt Cancer Center, Florida, USA, determined on page 571 if there are any differences in the zonal distribution and tumor volumes of familial and sporadic prostate cancers (PC) in men undergoing radical prostatectomy. After contacting 382 patients that filled the selection criteria, 76 (20%) reported having a first-degree relative with PC. The statistical analysis revealed no significant differences in the pathologic variables between the two groups of patients with or without a family history of PC. It was concluded that familial and sporadic PC share similar characteristics. No histopathological differences account for the increased positive predictive value of PC screening tests among patients with a family history of PC.

Dr. Leite and co-workers, from University of Sao Paulo Medical School, Sao Paulo, Brazil, reviewed on page 583 the characteristics of radical prostatectomies (RPs) when immunohistochemistry (IHC) was necessary for definitive diagnosis. Out of 4127 biopsies examined, 144 (3.5%) were

diagnosed with ASAP. IHC was performed using antibody anti-34βE12 and p63. The results of surgical specimens of 27 patients treated by RP after the diagnosis of prostate cancer (PC) was made using IHC (Group 1) were compared with 1040 patients where IHC was not necessary (Group 2). It was concluded that the use of IHC did not lead to diagnosis of insignificant tumors as illustrated by absence of differences in pathological stage or positive surgical margins in men submitted to RP. Therefore, the results suggested that this modality should be routinely used for a borderline biopsy and ASAP cases.

Dr. Kajbafzadeh and colleagues from Tehran University of Medical Sciences, Iran, investigated on page 614 the efficacy of transcutaneous functional electrical stimulation (FES) on voiding symptoms in children with myelomeningocele (MMC) suffering from neuropathic urinary incontinence. The authors studied 12 children with moderate to severe urinary incontinence secondary to MMC were included. They underwent an urodynamic study (UDS) before and 3 months after FES with special attention to detrusor leak point pressure and maximal bladder capacity (MBC). Fifteen courses of FES for 15 minutes 3 times per week were performed with low frequency (40 Hz) electrical current, duration of 250μs, with hold and rest time of 2 seconds. It was found that 9 children had improvement on urinary incontinence score, while 3 children had no improvement. The authors concluded that this pilot study showed that FES therapy might have positive effects on improvement of voiding symptoms of MMC children with neurogenic urinary incontinence in terms of daily incontinence score and UDS parameters.

Francisco J.B. Sampaio, M.D.
Editor-in-Chief

Review Article

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Is Male Infertility a Forerunner to Cancer?

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ABSTRACT

Purpose: The frequency of testicular cancer and male infertility has been increasing in the past several decades. This article examines the relationship between male infertility and testicular cancer, concentrating particularly on causal links.
Results: Both of these disorders are associated with testicular dysgenesis syndrome and have also been traced to mutations in genes involving DNA repair and tumor suppression, as well as environmental exposure.
Conclusion: The identification and examination of these common points of origin supports the integration of testicular cancer screenings into the routine evaluation of infertile men.

Key words: *male infertility; endocrine-disruption; testicular cancer; testicular dysgenesis*
Int Braz J Urol. 2010; 36: 527-36

INTRODUCTION

In recent years there has been a marked decline in male reproductive health. Concomitant with a decrease in semen quality, there has been a 3- to 4-fold increase in the incidence of genitourinary abnormalities and a 6-fold increase in the incidence of testicular cancer. Declines in semen quality have caused an increase in the population of infertile males. Recent studies have also shown that there is an increase in the incidence of gonadal tumors in infertile men. Therefore, there has been a growing concern that infertility may actually be a forerunner to or an early marker of testicular cancer.

Infertility and testicular cancer have been associated with one another as well as with genitourinary abnormalities including, cryptorchidism and hypospadias, and this triad of disorders constitutes a testicular dysgenesis syndrome (TDS). In this review, we will explore the various causal links between the components of TDS. The purpose of this article is to fortify the connection between infertility and testicular germ cell tumors by identifying their common origin, describing the incidence of disease states linking the two, and connecting carcinoma-in-situ (CIS) testis to both infertility and testicular cancer.

ETIOLOGY OF TESTICULAR CANCER

Risk Factors

Although many potential risk factors for germ cell tumors have been proposed, few have attained high levels of evidence in support of their association with testicular malignancies. Thus far, only cryptorchidism, contralateral testicular germ cell tumor, and familial history of testicular cancer have proven to be sound predictors of testicular cancer risk (1). A meta-analysis of 20 case control studies conducted by

Dieckmann and Pichlmeier found the relative risk of testicular germ cell tumors in individuals with a history of undescended testes to be 5 times greater than that of men without that history (1). In individuals with cryptorchidism, the risk of testicular cancer is also increased for the contralateral testes, providing support for the importance of testicular dysgenesis as a common point of origin (1). Familial history of testicular cancer confers a relative risk of 3-10, perhaps as a consequence of the inheritance of a susceptibility gene that has been identified on the X-chromosome (1). Additionally, patients with unilateral testicular germ cell tumors possess a much greater risk of developing a contralateral germ cell tumor (1). Three other factors twinship, testicular atrophy, and infertility, have also been associated with testicular germ cell tumors, but, so far, the evidence for these relationships has not been substantiated (1).

Carcinoma-in-situ Testis

Carcinoma-in-situ of the testis precedes the formation of all but two very rare forms of testicular cancer (2). In fact, fifty-percent or more of those individuals diagnosed with CIS will develop invasive testicular cancer within five years (2).

Genetically, CIS cells resemble embryonic stem cells, with their gene expression profile closely mirroring that of primordial germ cells and gonocytes but not that of infantile spermatogonia or adult germ cells (3). The proteins expressed in CIS cells are normally down-regulated during the transition from normal gonocytes to spermatogonia, suggesting that the origin of CIS cells is pre-meiotic in nature. It has been hypothesized that this is not the result of an inherent germ cell abnormality but, rather, inappropriate age signaling from surrounding cells, particularly Sertoli and Leydig cells, allowing continued germ cell expression of pluripotency and self-renewal genes. Gene up-regulation could also be the result of a failure of abnormal germ cells to undergo apoptosis. Both escape of cell cycle check points and improper age signaling could allow clonal proliferation of these abnormal cells, resulting in cells similar to those described in CIS.

Because fewer gonocytes are fully maturing to become spermatozoa in these instances, the total sperm count of men with CIS is lower, possibly resulting in sub-fertility. In support of this claim, impaired spermatogenesis has been observed in testes diagnosed with CIS (2). Similarly, the incidence of CIS in infertile men is 4-1.1% (4). This is strongly supportive of a link between infertility and testicular cancer.

MALE INFERTILITY

Male infertility and impaired spermatogenesis serve as one of the pillars of TDS. Infertility affects roughly 15% of couples, with 50% of the cases resulting from male factor (5). While the incidence of male infertility continues to rise, the majority of causes remain idiopathic. Both non-genetic and genetic factors contribute by influencing physiological processes related to spermatogenesis.

Genetic Causes

The most severe presentations of TDS, those that result in hypospadias, cryptorchidism, subfertility, and testicular cancer, are associated with genetic causes (6). In addition, genetic abnormalities are associated with approximately 15-30% of male infertility cases (7). Both of these disorders have been described in individuals with androgen insensitivity, 45X/46XY karyotype, and SRY mutations (6). Male infertility and testicular cancer have also been associated with defects in DNA repair genes, tumor suppressor gene mutations, and epimutations (8).

The 45X/46XY karyotype has been associated with a variety of medical conditions. Ambiguous genitalia and mixed gonadal dysgenesis are key features of this disorder (9). These patients are at increased risk for gonadal tumors, impaired fertility, and fibrosis as a result of ongoing gonadal changes (10). Most instances of this type of mosaicism are the result of a structural abnormality of or loss of the Y chromosome, specifically through nondisjunction following normal fertilization.

Mutations in the SRY gene have also been linked to gonadal tumor formation and infertility. Alterations of SRY are most commonly associated

with complete gonadal dysgenesis. These patients can present with phenotypes ranging from streak gonads like those seen in Turner syndrome to genital ambiguity. One meta-analysis noted gonadal tumor formation in 52.5% of patients with SRY abnormalities (11).

Spermatogenic impairment, infertility, and testicular cancer formation can also be associated with defects in DNA repair genes. Supraphysiological reactive oxygen species (ROS) levels in the semen have been well established to lead to oxidative damage to the sperm, which manifests as DNA breakage, cross-linkage, and mutations (12). Recent studies have shown that infertile men possess high ROS levels (12). In addition to the DNA damage caused, ROS also results in the production of highly mutagenic compounds that can further increase an individual's susceptibility to tumor formation (12).

Persistence of this damage is indicative of a deficiency in the DNA repair mechanisms. In addition, mutations in these repair genes can result in deletions or expansions of small repeat DNA sequences, unstable components that have been noted in many forms of cancer (13). Furthermore, these mutations and expansions of DNA repeat sequences can manifest as male infertility (13).

Cases of male infertility and cancer formation have also been attributed to deficiencies in tumor suppressor genes, particularly p53. Known to have a crucial role in tumor prevention and stress response pathways, p53 normally aides in coordinating a variety of cellular responses from cell cycle arrest and apoptosis to the maintenance of genomic stability. This gene also has an important role in spermatogenesis, specifically aiding in prophase of meiosis within primary spermatocytes. Mutations result in chromosomal and genomic instability, increasing the chance that p53 null cells will become malignant in nature and gain additional mutations (14).

Additionally, it has also been reported that p53 has a role in the up-regulation of certain antioxidant genes (15). Therefore, a mutation of this gene would certainly lead to higher levels of ROS, comparable to those seen in infertile males. Although there have been very few studies in humans on the effects of p53 mutations, knockout mice are infertile.

TESTICULAR DYSGENESIS SYNDROME

Testicular dysgenesis syndrome is one of several possible male reproductive health complications that could result from an aberrant developmental pathway. The components of TDS include low sperm count, hypospadias, cryptorchidism, and testicular cancer.

Incidence

The presentation of TDS is variable, with each of the symptoms present in differing degrees or one or more of them being absent entirely. Mild TDS has been estimated to affect 20% of the world's male population, while 5% of the population is thought to be afflicted with a more severe presentation in which all of the symptoms are present to a significant degree (16).

The increasing frequency of the individual health problems of TDS may suggest that these numbers are only going to get larger in the coming years. A recent study of eight populations with a long history of cancer registration saw the incidence of testicular cancer double in a twenty year period (17). In the same timeframe, there has been a marked decline in sperm density (18). Cryptorchidism and hypospadias are following a comparable temporal incline (19). These similarities have been taken as evidence for their linkage.

Evidence for the Linkage of the Three Presentations of TDS

In addition to these temporal trends, there have been many studies, especially from Scandinavian countries, that report geographic concentrations of these reproductive health problems. In Denmark, for example, twenty percent of the male population has suboptimal semen parameters, while sperm counts in nearby Finland have remained at a high level for the past few decades (20). In support of the existence of TDS, Danish men also exhibit higher incidences of congenital cryptorchidism and hypospadias, as well as a greater frequency of testicular cancer, than do Finnish men (21-23).

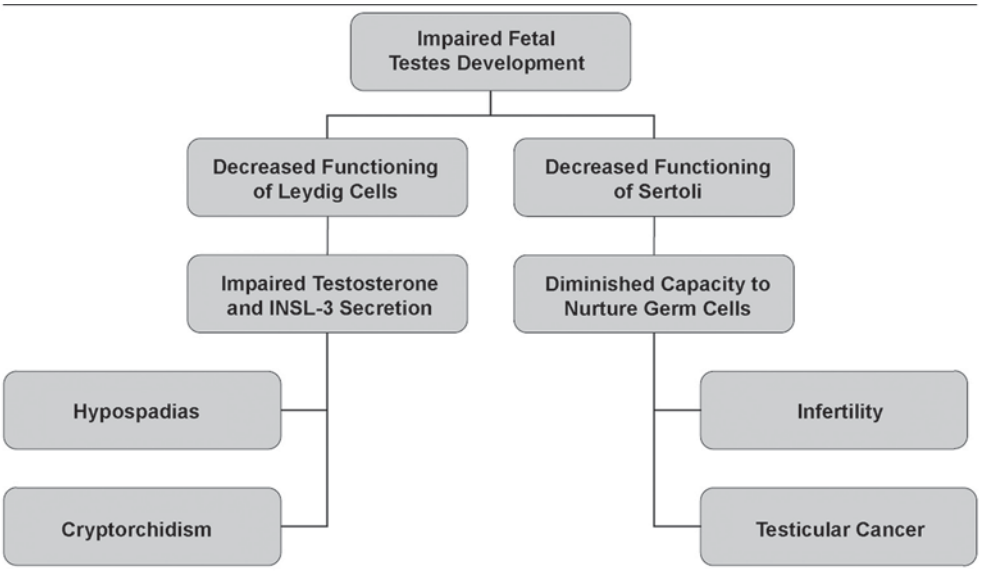

Figure 1 *– Proposed mechanism leading to testicular dysgenesis. In this pathway, the key event is the impairment of testes development during fetal life.*

Other studies have found very strong associations between two or more of the reproductive health disorders associated with TDS. For example, men with a history of cryptorchidism have a risk of testicular cancer that is 2-8 times that of those men without a history of undescended testes (1). Additionally, cryptorchidism is associated with impaired spermatogenesis and spermatogenic arrest, resulting in infertility (24). The congenital birth defects, cryptorchidism and hypospadias, which are manifestations of TDS are also very closely related to one another (25). The connection between infertility and testicular cancer is one that is still disputed, but many recent studies have found evidence to suggest that this link is particularly strong.

As suggested by the name of the disorder, testicular dysgenesis is the underlying correlation between the four presentations of this disease. Evidence of testicular dysgenesis in biopsies from patients with infertility or testicular germ cell tumors includes the presence of immature seminiferous tubules with undifferentiated Sertoli cells and Sertoli cell-only tubules (6). There have been several mechanisms proposed to explain the origins of these features, all of which rely upon the disruption of normal male differentiation during fetal development.

Proposed Pathway Leading to Testicular Dysgenesis

As the result of some genetic or environmental influence, normal development of the testes is impaired (Figure-1), resulting in improper functioning of the Sertoli and Leydig cells (26). The potential causes of this interruption are discussed below .

Improper Leydig cell function results in deficiencies in both testosterone and INSL-3 secretion. These two hormones are responsible for testicular descent. Therefore, it is highly likely that a disruption in their production could lead to cryptorchidism. In addition, because testosterone is the key hormone involved in the formation of male external genitalia, low testosterone levels lead to improper fusion of the urethral folds and hypospadias.

Intact and competent Sertoli cells are required for optimal spermatogenesis and spermiogenesis. Therefore, improper functioning of these cells leads to hypospermatogenesis and infertility (6). Additionally, the malfunctioning of Sertoli cells leads to the arrest of many gonocytes at an early stage of maturation. These arrested gonocytes are thought to be the forerunners to carcinoma in situ testis which, in turn, can develop into testicular germ cell cancer. Additionally, as a

consequence of decreased testosterone level, there will also be a diminished number of Sertoli cells, thereby compounding the problems associated with their malfunction.

The mechanism whereby testes development is interrupted remains to be identified, but both genetic and environmental factors have been implicated. The genetic causes have already been discussed in great length above. Therefore, an examination of environmental factors will be the main focus below.

Environment Factors and Testicular Dysgenesis

As previously mentioned, all the male reproductive health problems associated with TDS have greatly increased in frequency in the past several decades. A higher risk of testicular cancer and poor semen quality are closely associated with one's year of birth (27,28). This cohort phenomenon is strongly suggestive of some degree of environmental influence at work.

Environmental variables could be on the macroscopic scale. For example, geographic location of a mother during pregnancy can be indicative of her son's risk of TDS (6). Insults to the micro-environment of the fetus, however, can also play a substantive role in the development of the disease.

The environmental variable that is currently receiving the most attention as a possible mediating factor in the development of testicular dysgenesis is a group of compounds known as endocrine-disrupting chemicals or xenoestrogens. These are anti-androgenic agents which mimic estrogens.

Endocrine Disrupting Chemicals

Phthalates, gums, and paints are anti-androgenic chemicals that are ubiquitous in human life. They have been used as plasticizers in PVC products and are constituents in many infant toys, storage containers, and medical devices (29). While experts recommend that daily exposure be limited to 2 mg, with nearly 18 billion pounds of phthalates being produced per year, many individuals have occupational or medical exposures greatly in excess of these guidelines (29).

Although humans are generally exposed to the diester form of phthalates (Figure-2), their more pressing concern should be the monoester forms that these chemicals are converted into within the body. This monoester form is 10 times more toxic than the diester form, and has been found in detectable levels in 75% of the population, thereby greatly increasing the risk for male reproductive tract disorders like those of TDS (29).

Proposed Mechanism

These agents are believed to cause an increase in estrogen levels in the blood which, in turn, inhibits the hypothalamopitutary gonadal axis, resulting in decreased production of follicle stimulating hormone (FSH) and, subsequently, a fixing of Sertoli cell number.

In most mammals, Sertoli cell replication occurs only during fetal and post natal life. Sertoli cell number thus becomes fixed at a particular stage of development. However, in man, the Sertoli cell number increases significantly between late fetal and pre-pubertal life and also increases further during puberty. Hence the window for adverse effect on Sertoli cells in man is longer than that known for other mam-

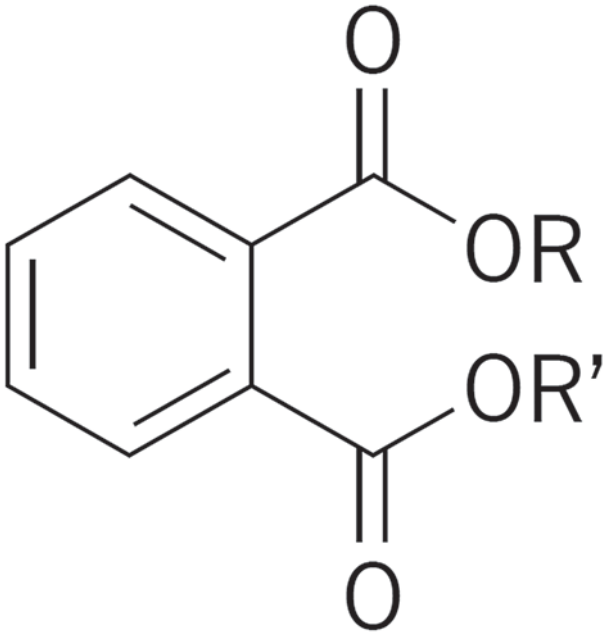

Figure 2 *– Generic diester phthalate.*

Table 1 *– Hormonal changes indicative of Leydig and Sertoli cell malfunction in testicular dysgenesis syndrome (TDS).*

	FSH	LH	Serum Testosterone
Cryptorchidism	Elevated	Elevated	--*
Hypospadias	Elevated	Elevated	--*
Infertility	--*	Elevated	Decreased
Testicular Cancer	Elevated	Elevated	Decreased

*Changes in hormonal Assays with the reproductive health problems of TDS; * Indicates where data was unavailable; FSH = follicle stimulating hormone; LH = luteinizing hormone.*

malian species. Thus, after exposure to environmental hormones, xenoestrogens, or environmental endocrine disruptors, these chemicals accumulate in the body, and their effects are biomagnified over a period of time.

Upon exposure to an endocrine disruptor, the resulting elevation in maternal and fetal estrogens inhibits FSH secretion, leading to decreased Sertoli cell number, lower levels of anti-Mullerian hormone, and decreased expression of SRY. This may result in abnormal sexual differentiation, leading to cryptorchidism and hypospadias, as well as hypospermatogenesis (30,31). It also eventually may lead to testicular cancer through a process known as hormonal carcinogenesis (32-34).

These findings were summarized by, Sharpe and Skakkebaek in a landmark article, now known as the "estrogen hypothesis", which linked exposure to exogenous estrogens to male reproductive tract disorders, including TDS (35).

While their precise effect on the male reproductive tract is poorly understood, phthalates and other endocrine-disrupting chemicals have been strongly correlated with each of the reproductive health problems associated with TDS in both human and animal studies. As this research becomes more thorough, our understanding of the mechanisms from which these disorders result will also become more clear.

Evidence from Human Retrospective Studies

Human retrospective studies have provided considerable evidence for the importance of endocrine disrupting chemicals in the induction of male reproductive health disorders. One potent source of synthetic estrogen exposure is pesticides, which are known to possess estrogenic, anti-androgenic, and aromatase inhibiting effects in vivo. It has been shown that maternal exposure to pesticides during pregnancy is associated with an increased risk of cryptorchidism in male infants (36). A separate study also found that women who worked in greenhouses while pregnant gave birth to sons with significant reproductive health impairment, particularly a three-fold greater risk of cryptorchidism (37).

Studies investigating the different hormone levels in males exhibiting one or more reproductive health problems have also been helpful in demonstrating the possible pathogenesis of TDS. Three month old male infants with cryptorchidism were shown to have significantly elevated levels of FSH and LH as well as reduced inhibin B concentrations compared with controls (38). Similar changes in hormone levels were also seen in boys with hypospadias (39). Additionally, lower serum testosterone levels have been reported in infertile men compared with proven fertile men. Infertile men in this study had a lower testosterone/LH ratio and higher serum LH levels as well (40). Higher levels of LH and FSH, in addition to lower serum testosterone levels, have also been seen in men with CIS and testicular cancer (41), Table-1.

Taken together, these hormonal changes are indicative of compensated Leydig cell failure. The pituitary gland releases LH to stimulate the Leydig cells to produce testosterone. When Leydig cells fail to properly receive or interpret this signal, the pituitary secretes more LH to compensate, resulting in high levels of LH and low levels of testosterone in the blood. Decreased androgen production that would accompany Leydig cell malfunctioning has recently

been shown to have a dramatic effect on the number of Sertoli cells in the perinatal period. Faulty nurse cells will be less capable of nurturing germ cells into mature spermatozoa, leading to poor semen quality in adulthood and also to germ cell maturation arrest, increasing the likelihood of developing CIS and testicular cancer. These changes are exactly those hypothesized to be involved in the pathogenesis of TDS (29,42,43).

Evidence from Animal Models

Several animal models have concentrated on the effects of different endocrine-disrupting compounds on male reproductive tract development in rats or mice. In a study published by Fisher et al., exposure to dibutyl phthalate in utero resulted in the abnormal function and distribution of all major cell types within the rat testis (44). This study described genital abnormalities at both the macroscopic and microscopic level that are similar to those disorders associated with TDS in humans, including cryptorchidism, hypospadias, incomplete seminiferous cord formation, and Sertoli cell-only tubules. Additionally, changes in the proportion of Sertoli cells seen within those males exposed to DBP rendered germ cells incapable of maturation and support of spermatogenesis (44). A similar study by Mahood et al., in which male rats were exposed to DBP in utero, resulted in decreased INSL-3 gene expression, multi-nucleated gonocytes, abnormal Leydig cell aggregation, and decreased testicular testosterone (45). The results of these two studies are indicative of severe testicular dysgenesis as a result of in utero exposure to endocrine-disrupting chemicals. Additional studies on rodents have shown similar results (29,42,43).

Because the negative effects of exposure to these chemicals are not evenly distributed among the treatment groups, there likely exists some degree of genetic predisposition for developing the male reproductive disorders associated with exposure. These findings lend credence to the assumption that TDS is a multi-factorial disease involving both a genetic and environmental contribution.

While animal models have provided much mechanistic insight into the role of endocrine disruptors in TDS, they have yet to observe testicular cancer in the treated animals. Therefore, the current belief that testicular cancer is connected to both the genital abnormalities and infertility attributed to TDS is reliant upon human retrospective studies and our current understanding of the fetal origins of these disorders and of testicular cancer itself.

TESTICULAR CANCER AND MALE INFERTILITY

Testicular dysgenesis syndrome proposes an association between testicular cancer, male infertility, and genital abnormalities. Due to the long time period over which these various disorders may appear, it is difficult to track the course of those potentially afflicted individuals longitudinally. More easily done, however, is to study the associations between testicular cancer and infertility, two male reproductive disorders that present at roughly the same time in an individual's life. The establishment of a definitive relationship between these two diseases could significantly decrease the incidence of testicular cancer if this association was indicative of a benefit to increased testicular cancer screening for infertile patients. Thus far, there have been many studies within the literature that focus on this relationship specifically.

Some studies have looked retrospectively at the pre-cancer fertility capacity of men that later developed testicular cancer. For example, it has been shown that men develop testicular cancer have fewer children than age-matched men who did not develop testicular cancer (46). Another study by Petersen and Skakkebaek analyzed the semen quality of men diagnosed with unilateral testicular cancer. This group reported that the quality of semen collected from these men was much poorer than would typically be expected for a man possessing one functional testicle (47). CIS is also seen more frequently in the testicular biopsies of men evaluated for sub-fertility or infertility (48). This would strongly suggest that men with fertility problems, even those that go undiagnosed with sub-fertility, are at an increased risk of developing testicular cancer.

Recent research has supported the existence of this increased risk, although the exact impact of

infertility or sub-fertility on testicular cancer risk is still disputed. A study by Jacobson et al. reported the increased risk of testicular cancer in men with fertility problems to be 1.6 times that of men with normal semen parameters (49). A more recent study by Raman estimated the incidence of testicular cancer in infertile men to be 20 times greater than that of proven fertile men (50).

Clinical Implications

The increased risk of testicular cancer associated with male infertility speaks strongly for the importance of incorporating testicular cancer screening into the routine care of infertile men. While the only definitive way to determine if testicular cancer is present is to perform a testicular biopsy, this test is invasive and may not be a practical way to screen a large population of infertile males. Scrotal ultrasonography can also detect the presence of tissue irregularities that might be indicative of testicular cancer or CIS. Perhaps the easiest way to provide testicular cancer screening to those suffering from male infertility is to teach them how to perform self-examinations. This would allow the patient to detect palpable changes in the testicular tissue that might precede testicular cancer.

CONCLUSION

The identification of testicular dysgenesis syndrome has established a connection between male infertility and testicular cancer. The reproductive health problems associated with this disorder are manifestations of improper testicular development during fetal life. Subsequent malfunctioning of both the Sertoli and the Leydig cells are responsible for the failure of gonocytes to mature properly, resulting in a lower number of mature spermatozoa and a greater likelihood of developing CIS. This common etiology, when combined with what is known about the genetic origins of male infertility and testicular cancer, is strongly suggestive of the link between these two disease states. As further research explores the relative influence of both genetics and the environment in the etiology of TDS and strengthens the connection between infertility and testicular cancer, the current research base provides compelling evidence for increasing testicular cancer screenings for infertile men. By integrating screenings into the routine evaluation of infertile men, it will be possible to detect cases of testicular cancer earlier, and, ultimately, decrease its incidence.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Dieckmann KP, Pichlmeier U: Clinical epidemiology of testicular germ cell tumors. World J Urol. 2004; 22: 2-14.
2. Rørth M, Rajpert-De Meyts E, Andersson L, Dieckmann KP, Fossa SD, Grigor KM, et al.: Carcinoma in situ in the testis. Scand J Urol Nephrol Suppl. 2000; 205: 166-86.
3. Almstrup K, Hoei-Hansen CE, Wirkner U, Blake J, Schwager C, Ansorge W, et al.: Embryonic stem cell-like features of testicular carcinoma in situ revealed by genome-wide gene expression profiling. Cancer Res. 2004; 64: 4736-43.
4. Cortes D, Thorup J, Frisch M, Møller H, Jacobsen GK, Beck BL: Examination for intratubular germ cell neoplasia at operation for undescended testis in boys. J Urol. 1994; 151: 722-5.
5. Poongothai J, Gopenath TS, Manonayaki S: Genetics of human male infertility. Singapore Med.J. 2009; 50: 336-347.
6. Wohlfahrt-Veje C, Main KM, Skakkebaek NE: Testicular dysgenesis syndrome: foetal origin of adult reproductive problems. Clin Endocrinol (Oxf). 2009; 71: 459-65.
7. Ferlin A, Raicu F, Gatta V, Zuccarello D, Palka G, Foresta C: Male infertility: role of genetic background. Reprod Biomed Online. 2007; 14: 734-45.

8. Paul C, Povey JE, Lawrence NJ, Selfridge J, Melton DW, Saunders PT: Deletion of genes implicated in protecting the integrity of male germ cells has differential effects on the incidence of DNA breaks and germ cell loss. PLoS One. 2007; 2: e989.
9. Achermann JC, Jameson JL: Disordes of Sex Development. In: Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J (eds.), Harrison's Principles of Internal Medicine. New York, Mc Graw Hill. 2008; 17th ed., pp. 2339.
10. Baskin LS: Abnormalities of Sexual Determination & Differentiation. In: Tanagho EA, McAninch JW (eds.), Smith's General Urology. New York, Mc Graw Hill. 2008; 17th ed., pp. 649.
11. Uehara S, Hashiyada M, Sato K, Nata M, Funato T, Okamura K: Complete XY gonadal dysgenesis and aspects of the SRY genotype and gonadal tumor formation. J Hum Genet. 2002; 47: 279-84.
12. Hughes CM, Lewis SE, McKelvey-Martin VJ, Thompson W: A comparison of baseline and induced DNA damage in human spermatozoa from fertile and infertile men, using a modified comet assay. Mol Hum Reprod. 1996; 2: 613-9.
13. Devouassoux-Shisheboran M, Mauduit C, Bouvier R, Berger F, Bouras M, Droz JP, et al.: Expression of hMLH1 and hMSH2 and assessment of microsatellite instability in testicular and mediastinal germ cell tumours. Mol Hum Reprod. 2001; 7: 1099-105.
14. Fenton RG, Longo DL: Cancer Cell Biology and Angiogenesis. In: Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J (eds.), Harrison's Principles of Internal Medicine. New York, Mc Graw Hill. 2008; 17th ed., pp. 498.
15. Tourtellotte WG, Nagarajan R, Auyeung A, Mueller C, Milbrandt J: Infertility associated with incomplete spermatogenic arrest and oligozoospermia in Egr4-deficient mice. Development. 1999; 126: 5061-71.
16. Boisen KA, Main KM, Rajpert-De Meyts E, Skakkebaek NE: Are male reproductive disorders a common entity? The testicular dysgenesis syndrome. Ann N Y Acad Sci. 2001; 948: 90-9.
17. Lacerda HM, Akre O, Merletti F, Richiardi L: Time trends in the incidence of testicular cancer in childhood and young adulthood. Cancer Epidemiol Biomarkers Prev. 2009; 18: 2042-5.
18. Swan SH, Elkin EP, Fenster L: The question of declining sperm density revisited: an analysis of 101 studies published 1934-1996. Environ Health Perspect. 2000; 108: 961-6.
19. Paulozzi LJ: International trends in rates of hypospadias and cryptorchidism. Environ Health Perspect. 1999; 107: 297-302.
20. Vierula M, Niemi M, Keiski A, Saaranen M, Saarikoski S, Suominen J: High and unchanged sperm counts of Finnish men. Int J Androl. 1996; 19: 11-7.
21. Richiardi L, Bellocco R, Adami HO, Torrang A, Barlow L, Hakulinen T, et al.: Testicular cancer incidence in eight northern European countries: secular and recent trends. Cancer Epidemiol Biomarkers Prev. 2004; 13: 2157-66.
22. Boisen KA, Kaleva M, Main KM, Virtanen HE, Haavisto AM, Schmidt IM, et al.: Difference in prevalence of congenital cryptorchidism in infants between two Nordic countries. Lancet. 2004; 363: 1264-9.
23. Boisen KA, Chellakooty M, Schmidt IM, Kai CM, Damgaard IN, Suomi AM, et al.: Hypospadias in a cohort of 1072 Danish newborn boys: prevalence and relationship to placental weight, anthropometrical measurements at birth, and reproductive hormone levels at three months of age. J Clin Endocrinol Metab. 2005; 90: 4041-6.
24. Cortes D, Thorup JM, Visfeldt J: Cryptorchidism: aspects of fertility and neoplasms. A study including data of 1,335 consecutive boys who underwent testicular biopsy simultaneously with surgery for cryptorchidism. Horm Res. 2001; 55: 21-7.
25. Weidner IS, Møller H, Jensen TK, Skakkebaek NE: Risk factors for cryptorchidism and hypospadias. J Urol. 1999; 161: 1606-9.
26. Rajpert-De Meyts E: Developmental model for the pathogenesis of testicular carcinoma in situ: genetic and environmental aspects. Hum Reprod Update. 2006; 12: 303-23.
27. Bergström R, Adami HO, Möhner M, Zatonski W, Storm H, Ekbom A, et al.: Increase in testicular cancer incidence in six European countries: a birth cohort phenomenon. J Natl Cancer Inst. 1996; 88: 727-33.
28. Irvine S, Cawood E, Richardson D, MacDonald E, Aitken J: Evidence of deteriorating semen quality in the United Kingdom: birth cohort study in 577 men in Scotland over 11 years. BMJ. 1996; 312: 467-71.
29. Ge RS, Chen GR, Tanrikut C, Hardy MP: Phthalate ester toxicity in Leydig cells: developmental timing and dosage considerations. Reprod Toxicol. 2007; 23: 366-73.
30. Docimo SG, Silver RI, Cromie W: The undescended testicle: diagnosis and management. Am Fam Physician. 2000; 62: 2037-44, 2047-8.
31. Lu CC, Steinberger A: Effects of estrogen on human seminiferous tubules: light and electron microscopic analysis. Am J Anat. 1978; 153: 1-13.

32. Fowler KA, Gill K, Kirma N, Dillehay DL, Tekmal RR: Overexpression of aromatase leads to development of testicular leydig cell tumors : an in vivo model for hormone-mediated TesticularCancer. Am J Pathol. 2000; 156: 347-53.
33. Skakkebaek NE, Rajpert-De Meyts E, Main KM: Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. Hum Reprod. 2001; 16: 972-8.
34. Weir HK, Marrett LD, Kreiger N, Darlington GA, Sugar L: Pre-natal and peri-natal exposures and risk of testicular germ-cell cancer. Int J Cancer. 2000; 87: 438-43.
35. Sharpe RM, Skakkebaek NE: Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract? Lancet. 1993; 341: 1392-5.
36. Pierik FH, Burdorf A, Deddens JA, Juttmann RE, Weber RF: Maternal and paternal risk factors for cryptorchidism and hypospadias: a case-control study in newborn boys. Environ Health Perspect. 2004; 112: 1570-6.
37. Andersen HR, Schmidt IM, Grandjean P, Jensen TK, Budtz-Jørgensen E, Kjaerstad MB, et al.: Impaired reproductive development in sons of women occupationally exposed to pesticides during pregnancy. Environ Health Perspect. 2008; 116: 566-72.
38. Suomi AM, Main KM, Kaleva M, Schmidt IM, Chellakooty M, Virtanen HE, et al.: Hormonal changes in 3-month-old cryptorchid boys. J Clin Endocrinol Metab. 2006; 91: 953-8.
39. Hsieh MH, Breyer BN, Eisenberg ML, Baskin LS: Associations among hypospadias, cryptorchidism, anogenital distance, and endocrine disruption. Curr Urol Rep. 2008; 9: 137-42.
40. Andersson AM, Jørgensen N, Frydelund-Larsen L, Rajpert-De Meyts E, Skakkebaek NE: Impaired Leydig cell function in infertile men: a study of 357 idiopathic infertile men and 318 proven fertile controls. J Clin Endocrinol Metab. 2004; 89: 3161-7.
41. Petersen PM, Giwercman A, Hansen SW, Berthelsen JG, Daugaard G, Rørth M, et al.: Impaired testicular function in patients with carcinoma-in-situ of the testis. J Clin Oncol. 1999; 17: 173-9.
42. Ferrara D, Hallmark N, Scott H, Brown R, McKinnell C, Mahood IK, et al.: Acute and long-term effects of in utero exposure of rats to di(n-butyl) phthalate on testicular germ cell development and proliferation. Endocrinology. 2006; 147: 5352-62.
43. Gray LE Jr, Wilson VS, Stoker T, Lambright C, Furr J, Noriega N, et al.: Adverse effects of environmental antiandrogens and androgens on reproductive development in mammals. Int J Androl. 2006; 29: 96-104; discussion 105-8.
44. Fisher JS, Macpherson S, Marchetti N, Sharpe RM: Human 'testicular dysgenesis syndrome': a possible model using in-utero exposure of the rat to dibutyl phthalate. Hum Reprod. 2003; 18: 1383-94.
45. Mahood IK, Scott HM, Brown R, Hallmark N, Walker M, Sharpe RM: In utero exposure to di(n-butyl) phthalate and testicular dysgenesis: comparison of fetal and adult end points and their dose sensitivity. Environ Health Perspect. 2007; 115 (Suppl 1): 55-61.
46. Møller H, Skakkebaek NE: Risk of testicular cancer in subfertile men: case-control study. BMJ. 1999; 318: 559-62.
47. Petersen PM, Skakkebaek NE, Giwercman A: Gonadal function in men with testicular cancer: biological and clinical aspects. APMIS. 1998; 106: 24-34; discussion 34-6.
48. Olesen IA, Hoei-Hansen CE, Skakkebaek NE, Petersen JH, Rajpert-De Meyts E, Jørgensen N: Testicular carcinoma in situ in subfertile Danish men. Int J Androl. 2007; 30: 406-11; discussion 412.
49. Jacobsen R, Bostofte E, Engholm G, Hansen J, Olsen JH, Skakkebaek NE, et al.: Risk of testicular cancer in men with abnormal semen characteristics: cohort study. BMJ. 2000; 321: 789-92.
50. Raman JD, Nobert CF, Goldstein M: Increased incidence of testicular cancer in men presenting with infertility and abnormal semen analysis. J Urol. 2005; 174: 1819-22; discussion 1822.

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Review Article

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Radical Cystectomy with Orthotopic Neobladder for Invasive Bladder Cancer: A Critical Analysis of Long Term Oncological, Functional and Quality of Life Results

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ABSTRACT

Purpose: Analyze current knowledge and practice regarding tumor-related cystectomy with subsequent orthotopic neobladder both in male and female patients.
Design, setting, and participants: Evaluate literature predominantly from the last decade dealing with long-term experience in large numbers of patients with an orthotopic neobladder following cystectomy. Oncological outcome specific to an orthotopic neobladder, functional aspects such as urinary continence, renal function, sexual activity and other quality of life issues are elucidated.
Results: Local pelvic recurrences after urothelial bladder cancer occur in 7-12%. Urethral second primary tumors in male and female patients in contemporary series with bladder substitution are 4-6% and 1.4 o 4%, respectively. Upper tract recurrences vary between 2.4-17%. Complications regarding the upper urinary tract have dramatically diminished due to simplified forms of upper tract protection as well as a more refined technique of ureterointestinal anastomosis. Depending on the technique ureteroileal stenosis was lately reported to lie between 2.7 to 3.8%. Renal function remained stable in 96% after a mean follow-up of up to 5 years.
Conclusion: Radical cystectomy in carefully selected patients has stood the test of time by providing adequate long-term survival and low local recurrence rates. Orthotopic bladder substitution does not compromise oncological outcome, yields excellent functional results, is cost effective compared to other types of urinary diversion, may improve quality of life and should therefore be the diversion of choice both in men and women. Chronological age is generally not a contraindication for cystectomy, but for orthotopic urinary diversion, tumor extent, functional pelvic floor deficits and general life expectancy are limiting factors.

Key words: *bladder neoplasms; cystectomy; urinary diversion; quality of life, oncology*
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INTRODUCTION

Apart from the oncological outcome an important aspect after bladder removal nowadays is the type of urinary diversion and its selection in various patients. Aspects addressed in modern day urinary diversion included the segment and type of reconfiguration of the gastrointestinal tract used, the anatomical location of a possible stoma, preservation of the urethra for an orthotopic diversion, the issue of an upper urinary tract protection and gender specific differences (1).

With improvement of oncological results, quality of life aspects such as continent urethral

(orthotopic) diversion, and preservation of sexual activity became more important. In order to improve functional outcome to an acceptable level several authors have evaluated and identified the exact anatomical localization of autonomic nerves within the pelvis. Landmarks and strategies were described to preserve these structures and thereby guarantee an unaffected postoperative sexual activity in male as well as in female patients. Meticulous dissection of the bladder neck and adjacent proximal urethra with utmost preservation of both the external sphincter (rhabdosphincter) and a remnant portion of the urethral smooth musculature were of uppermost importance for postoperative continence and voiding. Furthermore, it has been suggested that in patients with an orthotopic bladder substitution preservation of autonomic nerves contributes to maintenance of continence and intact voiding function (2). A recent WHO consensus conference on bladder cancer treatment has shown that the orthotopic bladder substitution to the urethra is the most commonly used diversion in the majority of centers with emphasis on surgical treatment of bladder cancer. However, considerable regional differences exist regarding type of urinary diversion and its modifications (3).

With a clinical experience expanding over several decades now with orthotopic bladder substitution following bladder malignancy driven cystectomy the present contribution focuses on long-term data regarding oncological, functional and quality of life aspects.

ONCOLOGICAL ASPECTS

Overall 5- and 10-year recurrence-free survival in organ-confined disease in contemporary large series is 62-68% and 50-66%, respectively (2-6), Table-1. Without treatment, about 85 % of patients with muscle - invasive bladder cancer die within the first 2 years following initial diagnosis (7). Compared to other treatment strategies it has become clear over the last decades that radical cystectomy is the standard of care in high grade invasive bladder tumors, because it provides the highest survival as well as the lowest recurrence rates in these patients (3,5,8-10). Several oncological and technical aspects, however, such as the necessary extent of lymphadenectomy, its diagnostic and therapeutic potential, the type of urinary diversion (e.g. ileal conduit vs. orthotopic neobladder substitution), and the impact of urethral preservation on the likelihood of urethral or local recurrences following radical cystectomy are still under discussion.

In the biggest single institution series on outcome of cystectomy in 1054 patients with a more than 10-year median survival Stein et al. reported a 5- and 10-year recurrence-free survival for patients with organ-confined, lymph node-negative tumors of 92% and 86% for P0 disease, 91% and 89% for Pis, 79% and 74% for Pa, and 83% and 78% for P1 tumors, respectively. Patients with muscle invasive (P2 and P3a), lymph node-negative tumors had 89% and 87% and 78% and 76% 5-and 10-year recurrence-free survival, respectively. Patients with nonorgan-confined (P3b, P4), lymph node-negative tumors with or without adjuvant treatment demonstrated a significantly higher probability of recurrence compared with those with organ-confined bladder cancers ($P < 0.001$). In those patients selected for surgery due to presumably localized disease 5- and 10-year recurrence-free survival for P3b tumors was 62% and 61%, and for P4 tumors was 50% and 45%, respectively (11).

Prostate and seminal vessel sparing cystectomy appears to be an attractive alternative to standard total cystoprostatectomy concerning sexual function and fertility. However, these advantages come at a price, i.e. a 10 to 15% higher oncological failure rate (12).

LYMPH NODE INVOLVEMENT AT THE TIME OF CYSTECTOMY

Lymphogenic metastatic spread already present at the time of surgery plays a major prognostic role but may be strongly correlated to an underlying T-stage (Table-2). (5,11,13,14). Apart from lymphnodular tumor manifestation the number of positively infiltrated lymph nodes was identified as parameter of prognostic relevance.

The question whether the total number of removed nodes regardless of node involvement

Table 1 *– Largest single institution studies looking at recurrence free survival rates after cystectomy.*

Reference	N of Patients (male + female)	Follow-up Median (months)	Recurrence Free Survival		Recurrence	
			5 years (%)	10 years (%)	Local only (%)	Distant only (%)
Stein (4)	1054	122	68	66	7	22
Madersbacher (5)	507	45	62	50	8	35
Hautmann (6)	788	53	65	59	9	18

increases the likelihood of detecting occult nodal metastases remains a controversially discussed issue. Herr (15) argued that the probability of detecting lymph node metastases might correlate with the total number of removed nodes. Others have correlated outcome to the number of involved nodes and their location (16,17). Five-year disease-specific survival rates for radical cystectomy patients with lymph node metastases confined to the pelvis was reported to range between 7 and 32%. Minimal node involvement (N1) in organ - confined bladder tumors was not an adverse prognostic situation whereas bulky nodal disease (N3) did significantly affect prognosis in these patients (18). The number of nodes involved with a cut-off ranging from 5 to 8 lymph nodes affected by metastatic disease was a significant factor for survival according to several studies (11,13,19). Using the TNM criteria the 5 - year survival rate of N1 / N2 and N3 patients was 35 % and 17%, respectively (15,19). Using a cut-off number of involved lymph nodes of 8, Stein et al. were able to identify number of positive nodes as an independent parameter predicting clinical outcome (5).

The predictive value of the ratio between negative nodes and lymph nodes harboring metastases (≤ 20% / > 20%) to predict the patients' clinical prognosis has been suggested (15). The 5-year survival in patients with N+ disease and a lymph node density of < 20% was 64%, which is significantly higher than the 5-year survival of 8% for a comparable group of patients with a lymph node density of > 20%. Unfortunately none of the studies addressed the issue of individual anatomical differences in the number of (normal) pelvic lymph nodes (4,12,13,15,16). Thus, only a statement about "surgical" lymph node density, i.e. involved lymph nodes in relation to removed nodes, but not about the actual percentage of involved lymph nodes in individual patients is possible.

Ghoneim et al. (5) in a prospective study on 200 patients examined the value of an extended lymphadenectomy above the iliac bifurcation. There were no skipped lesions indicating that negative internal iliac and obturator nodes made a more proximal dissection unnecessary.

In summary, there is evidence that the number of lymph nodes removed, the number of positive nodes and tumor load within the lymph nodes have prognostic value in bladder cancer patients. Minimal nodal disease in organ-confined cancer may have a favorable clinical prognosis approximating that of patients with no detectable lymph node metastases

Table 2 *– Incidence of histologically proven positive lymph nodes (N+) at various pathological T-stages (4,16-18).*

	N+ (%)
pTis	1 - 4
pT1	10 - 13
pT2	15
pT3a	24
pT3b	43
pT4a+b	46

in the same T-stage. Prospective randomized studies examining the recommended extension of lymphadenectomy during cystectomy have to be awaited to draw conclusions in that regard.

ORTHOTOPIC URINARY DIVERSION AND TUMOR RECURRENCE

Overall, the recurrence rate in larger series of high grade, invasive TCC, irrespective of urinary diversion ranges from 27% to 43%. Eighty-six percent of all recurrences occur within 36 months following surgery, with an average interval from surgery of 12 months (4). Late recurrences at unusual sites such as the central neural system after an interval of more than 5 years have been reported especially in the setting of patients who received neoadjuvant or adjuvant chemotherapy suggesting the need for a life-long follow-up (20).

The most worrisome question in orthotopic bladder substitution is whether second primary tumors in the urothelium covered segments of the remnant urethra are frequent and might be an oncological risk for the patient. It has been demonstrated that second primary tumors of the urethra are less frequent in orthotopic neobladders than in the blind ending urethra of abdominal diversions, and are reported to occur in 5-9% (21). Studer et al. (20) reported urethral second primary tumor rate of 5% in a series of 442 male and 40 female patients following cystectomy and orthotopic bladder substitution. Average time from surgery to recurrence was 14 months (range 3 to 158). Secondary urethrectomy was performed in 5 of the 482 patients (1%) and a conservative treatment was attempted in 13 cases, 2 of them requiring urethrectomy thereafter. For the whole cohort of neobladder patients suffering from urethral tumor recurrence, the median overall survival decreased to 38 months and 14 patients (2.9%) died from systemic tumor progression.

In a retrospective series of 768 male patients by Stein et al. (21) overall second primary tumor rate was 6%, irrespective of urinary diversion. In a multivariate statistical analysis, prostatic involvement by the primary tumor as well as cutaneous urinary diversion were independently associated with an increased risk for the development of second primary tumors. The calculated risk of second primary tumors was 5 and 9% for patients with an orthotopic and cutaneous urinary diversion, respectively. A difference for second primary tumors depending on initial prostatic tumor involvement was apparent for both superficial (12 vs. 5%) and invasive transitional cell carcinoma (TCC) (18 vs. 5%). A protective effect of urine in contact to the urethra, a reduction of bacterial cancerogenesis or a selection bias could be reasons for the more favorable urethral tumor rate in neobladder patients.

The hypothesis that female patients harbor an increased risk for the development of second primary tumors and should therefore have a mandatory urethrectomy as an integral part of cystectomy has been abandoned more than a decade ago. The incidence of second primary tumors in females subjected to orthotopic neobladder substitution is comparable to male series and predictive (22-24). In 841 female patients followed for more than 20 years, the urethral tumor rate was 2%. All patients with urethral tumors had primary tumors located at the bladder neck and/or the trigone in the.

In a series reported by Hautmann et al. (25) of 643 male and female neobladder patients, local pelvic recurrences and urethral recurrences were observed in 10% and 2% of cases, respectively. Voiding function was compromised in 2% of cases. Even in these 2% of the patients where outlet obstruction occurred it could be treated with intermittent self catheterization, chemotherapy, radiotherapy and/or resection.

Entero-enteral and entero-reservoir fistulas mainly due to preoperative radiotherapy, use of stapler devices, or local tumor recurrence have been described to affect up to 2% of patients (20,26). Non-tumor related and possibly some of the tumor related entero-reservoir fistulas may be prevented with the use of omentum or omental flaps at the time of initial surgery (27).

In contemporary series, second primary tumors of the upper tract in patients with urinary diversion due to TCC occur in 2.4 - 17 % of patients after an average time interval between 8 and 69 months with the biggest series of 1069 patients reporting an incidence of 2.5% and a median survival of 1.7 years

(range 0.2-8.8) (28). Upper tract recurrences more than 10 years after cystectomy have been observed (29).

In conclusion, tumor recurrence both in the urethra and in the upper urinary tract following orthotopic bladder replacement is acceptably low and should therefore per se not influence a decision towards a heterotopic diversion.

CONTINENCE AND URINARY RETENTION IN MALE PATIENTS

In using detubularized intestinal segments for construction of a low pressure reservoir aiming at a filling capacity of approximately 400-500 mL, continence is mainly achieved by utmost preservation of the urethral sphincter and its innervation. The rhabdosphincter in the male is not a circular structure limited to the prostatic apex but extends cranially along the ventral prostatic surface all the way to the bladder neck (30). By making every effort to carefully dissect this ventral portion off the prostate a larger amount of striated muscle cells can be preserved. Autonomic nerve preservation has shown to further improve continence by preserving afferent sensory nerves to the membranous urethra (31). Day - time continence defined as 0-1 pads per day was achieved in 88-95% of male and female patients after a minimum follow-up of one year in recent series (32-34). Night-time continence - depending on definition and management of the patients is usually lower, ranging from 66 to 93% (5,20,26,35). Over time, continence seems to decrease slightly, possibly to a decreased muscle tone and number of muscle cells the external rhabdosphincter related to changes with age (5,20,36,37). Nerve sparing surgical approaches as outlined above seem to improve the continence following orthotopic neobladder substitution both in male and female patients (36,38). A significantly longer functional urethral length and a higher maximal urethral pressure have been observed in patients undergoing nerve preservation in comparison to a non nerve-sparing control group (39). In neobladder patients preservation of autonomic innervation and age are the predominant factors affecting functional outcome (31).

In a large series with a follow-up of up to two decades Studer et al. observed residual urine volumes of more than 100 mL in 22% of all male and female neobladder patients (20). Urethral anastomotic strictures occurred in 3.7%, an occluding protrusion of the ileal mucosa over the neobladder outlet (termed ileal valve (27)) in 7%, and obstruction due to subtotal resection of the prostate in 1.7% of all patients.

The majority of the patients could be treated endoscopically. Two percent of the patients remained on a permanent catheter and 2.9% were instructed to perform intermittent self-catheterization (20). Hautmann et al. reported transient or permanent retention in 4 % of male patients (25), Abol-Enein found an infravesical obstruction in 3 % in a series of 344 evaluated male patients with a mean follow up of 38 months (40).

ONCOLOGICAL AND FUNCTIONAL OUTCOME IN FEMALE PATIENTS

Long term results in a growing number of female patients with orthotopic bladder substitution have verified that removing the bladder neck and a small portion of adjacent urethra but leaving a large portion of the urethra will not compromise oncological outcome (41).

In altogether 230 female bladder cancer patients with an orthotopic bladder substitution second primary tumors were observed in 1.4 to 4.3 % of women after a mean follow-up of 36 to 50 months (42,43).

Diurnal and nocturnal continence rates ranging from 82-95% and 72-86% respectively (32,44,45) were comparable to male patients. This continence rate despite the shorter remnant urethra used as neobladder outlet compared to male patients is remarkable and in some series may be partially the result of preservation of afferent and efferent autonomic nerves supplying urethral smooth musculature.

Removal of the bladder neck and an adjacent short segment of urethra is not only beneficial from an oncological standpoint but also improves outcome regarding volitional voiding (27).

The increased rates of urinary retention seen in female compared to male neobladder patients may be manifold. Leaving a too long segment of urethra might result in too much resistance for a low pressure intestinal reservoir. In an early series of women undergoing cystectomy without removing the entire bladder neck and subsequent orthotopic bladder substitution a majority of patients went into urinary retention (46). Preservation of autonomic nerves supplying the remnant urethra during cystectomy will not only reduce apoptosis of smooth muscle cells (30) but might also preserve the shortening and widening of the urethra thus facilitating volitional voiding.

The wider female pelvis and a shorter distance between mesenteric origin and urethra may be responsible for the phenomenon of the "ileal valve" mechanically obstructing the neobladder outlet predominantly in women (27). Whether a reduced angulation between neobladder floor and urethra leads to an increased retention rate and whether a correction or prevention with omentum, position sutures or vaginal suspension may play a role is still a matter of debate. Contemporary larger series report urinary retention and intermittent self-catheterization rates in 15 to 25% (21,32,47) where the bladder neck was removed and autonomic nerve preservation was attempted, and up to 50% where no explicit nerve preservation was done (25).

INTESTINAL RESERVOIR AND URETEROINTESTINAL CONNECTION

A recently published WHO consensus report summarizes a contemporary frequency distribution of various forms and techniques of urinary diversions in > 7000 patients with cystectomy. Forty-seven percent of male and female patients in the participating institutions received an orthotopic neobladder which was thus the most frequently used type of diversion (3).

The preferred type of bowel in the largest recent series dealing with orthotopic urinary diversion is terminal ileum (4,25). Arguments in favor of colonic segments such as the reduced length of bowel necessary to achieve an adequate volume, the use of the ileocecal valve as an antireflux mechanism, and a reduced rate of long term urinary retention have been proposed (48,49). However, less metabolic consequences and dysentery, easier surgical technique, better nocturnal continence rates, and a better functional protection of the upper urinary tract may have lead to the wide adoption of the ileal neobladder (2,50).

Ureteroilial stenosis was reported to occur in 2.7% of patients with an afferent tubular segment (20) and in 3.8% of patients with a serosa - lined extramural tunnel technique (40). Anatomical considerations leading to a meticulous vascularization sparing surgical technique (51) are important for a good outcome (52). Preference should be given to those techniques which will enable transurethral access to the upper tract in case of tumor recurrence, lithiasis and other endoscopically correctable problems in the upper urinary tract (52).

Long-term protection of renal function in bladder substitution could be demonstrated in the vast majority of patients. Anastomosing the ureters onto an afferent tubular segment rising serum creatinine levels were observed after a 5-year follow-up in 3.8% of cases (20). With the serosa - lined extramural tunnel technique renal function was preserved in 96.2% of patients after a mean follow-up of 38 months (40).

QUALITY OF LIFE

Heningssohn et al. (53) evaluated the quality of life in a cohort of patients subjected to radical cystectomy and orthotopic bladder substitution. The subjective global quality of life of 101 consecutive, recurrence - free bladder patients were comparable to a matched non-operated control group. Hobisch et al. (54) found that quality of life was preserved to a higher degree with an orthotopic neobladder compared to an ileal conduit urinary diversion in 102 male and female patients with a mean follow-up of 37 months. Other studies comparing different types of urinary diversion (incontinent vs. continent vs. orthotopic diversion) were unable to confirm a superior quality of one type of reconstruction over the others with regard to quality of life (55-57). An important proposed reason for this is that patients are subjected preoperatively to method-to-patient matching, and thus are prepared for disadvantages associated with different methods (3).

Distress in patients after cystectomy and continent urinary diversion in general was due to a compromised sexual function, urinary problems and bowel dysfunction (53).

SEXUAL ACTIVITY

Similar to continence and micturition potency and sexual activity are strongly correlated with autonomic nerve preservation and potency. Schoenberg et al. reported a correlation between age and potency in nerve sparing cystectomy in a 10-16 year experience with 101 male patients reporting a potency rate of 62% in men 49 years and younger, which decreased to 20% in men 70-79 years old (58). This was confirmed by several other studies. In a series from Berne by Kessler et al. comprising of 331 men (31) after a mean follow-up of 24 months recovery of erectile function was significantly more frequent in younger patients (< 65 years) and those with preserved autonomic nerves. In a subsequent larger group of patients the same group reported an overall potency rate (including those with medical assistance) of 38 % (20). In a smaller study from Japan 51 % of men age 40 to 59 years were able to have sexual intercourse (59).

With regards to female cystectomy various studies showed a deterioration of sexual function after radical cystectomy (60,61) with only half of the patients reporting to have successful sexual intercourse. The most common complaints of the women still practicing sexual intercourse were inability to receive orgasms, decreased vaginal lubrication, decreased sexual desire and dyspareunia (61). A single study compared sexual function in female patients after nerve sparing cystectomy and non nerve-sparing approaches (62). In this small study, the patients in the nerve sparing group showed only a minimal decline in Female Sexual Function Index , whereas the women in the non-nerve sparing group showed a significant decline.

METABOLIC CHANGES

The utilization of bowel for urinary diversion interferes with the physiological renal acid and salt regulation. Meticulous monitoring, careful electrolyte balance as well as sufficient hydration within the first postoperative time help to avoid dehydration and electrolyte depletion (63). Osteoporosis and osteomalacia might theoretically develop from a persistent hypokalemic, hyperchloremic acidosis. A transient acidosis developing postoperatively is common and should be controlled by usually oral intake of sodium bicarbonate. Within 4 years of the operation, reabsorption of metabolic substances of intestinal reservoirs and thereby the extent of metabolic problems associated with neobladder substitution significantly decreased (64).

In a recent investigation by Studer et al. abnormal bone density could not be observed in well-monitored patients for whom a follow-up of at least 10 years was available. In larger series including 314 patients where terminal ileum was used to substitute the urinary tract decreased Vitamin B12 levels required a substitution in 5% of cases (20). It is therefore suggested that surgical exclusion of the terminal ileum necessitates regular checking and at times substitution of Vitamin B12 after a follow-up of more than 5 years.

ELDERLY PATIENTS

In those elderly patients, defined as patients older than 75 to 80 years, which had been selected for surgery mortality and complication rates were similar compared to younger patients. Thus, chronological age is not a contraindication for radical cystectomy with curative intent, provided patients are selected carefully, and a preoperative risk assessment is done combined with a non-oncological life expectancy evaluation which should exceed 2 years (65).

Clark et al. (66) in a retrospective review of 1054 patients with cystectomy for curative intent and a median follow-up of 10.2 years found a similar mortality as well as diversion related complication rate in age groups less than 60 (n = 309), 60-69 (n = 381), 70-79 (n = 314) and 80 years or older. The operative mortality rates were 1%, 3%, 4% and 0% in each group. A lower proportion of patients older than 80 years underwent an orthotopic diversion. Three

and 5-year overall survival rates of 60% and 53% in patients aged 70 or older compared to 68% and 63%, respectively, in patients younger than 70 years were seen in this large retrospective study (67).

CONCLUSION

After more than 3 decades of clinical experience, orthotopic bladder substitution subsequent to radical cystectomy has stood the test of time by providing adequate long-term survival and low local recurrence rates. Orthotopic bladder substitution does not compromise oncological outcome, yields excellent functional results, is cost effective compared to other types of urinary diversion, may improve quality of life and should therefore be the diversion of choice both in men and women. Chronological age is generally not a contraindication for cystectomy, but for orthotopic urinary diversion, a careful patient selection considering tumor extent, patient motivation, preoperative sphincter function, other local and systemic adverse confounding factors and overall life expectancy must be taken into account. Minimally invasive techniques are promising concepts for the future, awaiting confirmation in larger patient cohorts.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Hendren WH: Historical perspective of the use of bowel in urology. Urol Clin North Am. 1997; 24: 703-13.
2. Stenzl A, Cowan NC, De Santis M, Jakse G, Kuczyk MA, Merseburger AS, Ribal MJ, Sherif A, Witjes JA: The updated EAD guidelines on muscle-invasive and metastatic bladder cancer. Eur Urol 2009; 55: 815-525.
3. Hautmann RE, Abol-Enein H, Hafez K, Haro I, Mansson W, Mills RD, et al.: For the WHO, Consensus Conference on Bladder Cancer "Urinary diversion" Urology. 2007; 69 (1 Suppl): 17-49.
4. Stein JP, Lieskovsky G, Cote R, Groshen S, Feng AC, Boyd S, et al.: Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. J Clin Oncol. 2001; 19: 666-75.
5. Madersbacher S, Hochreiter W, Burkhard F, Thalmann GN, Danuser H, Markwalder R, et al.: Radical cystectomy for bladder cancer today--a homogeneous series without neoadjuvant therapy. J Clin Oncol. 2003; 21: 690-6.
6. Hautmann RE, Gschwend JE, de Petriconi RC, Kron M, Volkmer BG: Cystectomy for transitional cell carcinoma of the bladder: results of a surgery only series in the neobladder era. J Urol. 2006; 176: 486-92; discussion 491-2.
7. Prout GR, Marshall VF: The prognosis with untreated bladder tumors. Cancer. 1956; 9: 551-8.
8. Stein JP: Indications for early cystectomy. Urology. 2003; 62: 591-5.
9. Montie JE: Against bladder sparing: surgery. J Urol. 1999; 162: 452-5; discussion 455-7.
10. Shipley WU, Kaufman DS, Heney NM, Althausen AF, Zietman AL: An update of selective bladder preservation by combined modality therapy for invasive bladder cancer. Eur Urol. 1998; 33(Suppl 4) :32-4.
11. Stein JP, Cai J, Groshen S, Skinner DG: Risk factors for patients with pelvic lymph node metastases following radical cystectomy with en bloc pelvic lymphadenectomy: concept of lymph node density. J Urol. 2003; 170: 35-41.
12. Hautmann RE, Stein JP: Neobladder with prostatic capsule and seminal-sparing cystectomy for bladder cancer: a step in the wrong direction. Urol Clin North Am. 2005; 32: 177-85.
13. Lerner SP, Skinner E, Skinner DG: Radical cystectomy in regionally advanced bladder cancer. Urol Clin North Am. 1992; 19: 713-23.
14. Vazina A, Dugi D, Shariat SF, Evans J, Link R, Lerner SP: Stage specific lymph node metastasis mapping in radical cystectomy specimens. J Urol. 2004; 171: 1830-4.
15. Herr HW: Superiority of ratio based lymph node staging for bladder cancer. J Urol. 2003; 169: 943-5.

16. Abdel-Latif M, Abol-Enein H, El-Baz M, Ghoneim MA: Nodal involvement in bladder cancer cases treated with radical cystectomy: incidence and prognosis. J Urol. 2004; 172: 85-9.
17. Leissner J, Hohenfellner R, Thüroff JW, Wolf HK: Lymphadenectomy in patients with transitional cell carcinoma of the urinary bladder; significance for staging and prognosis. BJU Int. 2000; 85: 817-23.
18. Vieweg J, Gschwend JE, Herr HW, Fair WR: Pelvic lymph node dissection can be curative in patients with node positive bladder cancer. J Urol. 1999; 161: 449-54.
19. Mills RD, Turner WH, Fleischmann A, Markwalder R, Thalmann GN, Studer UE: Pelvic lymph node metastases from bladder cancer: outcome in 83 patients after radical cystectomy and pelvic lymphadenectomy. J Urol. 2001; 166: 19-23.
20. Studer UE, Burkhard FC, Schumacher M, Kessler TM, Thoeny H, Fleischmann A, et al.: Twenty years experience with an ileal orthotopic low pressure bladder substitute--lessons to be learned. J Urol. 2006; 176: 161-6.
21. Stein JP, Clark P, Miranda G, Cai J, Groshen S, Skinner DG: Urethral tumor recurrence following cystectomy and urinary diversion: clinical and pathological characteristics in 768 male patients. J Urol. 2005; 173: 1163-8.
22. Stein JP, Esrig D, Freeman JA, Grossfeld GD, Ginsberg DA, Cote RJ, et al.: Prospective pathologic analysis of female cystectomy specimens: risk factors for orthotopic diversion in women. Urology. 1998; 51: 951-5.
23. Stenzl A, Draxl H, Posch B, Colleselli K, Falk M, Bartsch G: The risk of urethral tumors in female bladder cancer: can the urethra be used for orthotopic reconstruction of the lower urinary tract? J Urol. 1995; 153: 950-5.
24. Coloby PJ, Kakizoe T, Tobisu K, Sakamoto M: Urethral involvement in female bladder cancer patients: mapping of 47 consecutive cysto-urethrectomy specimens. J Urol. 1994; 152: 1438-42.
25. Hautmann RE, Volkmer BG, Schumacher MC, Gschwend JE, Studer UE: Long-term results of standard procedures in urology: the ileal neobladder. World J Urol. 2006; 24: 305-14.
26. Hautmann RE, de Petriconi R, Gottfried HW, Kleinschmidt K, Mattes R, Paiss T: The ileal neobladder: complications and functional results in 363 patients after 11 years of followup. J Urol. 1999; 161: 422-7; discussion 427-8.
27. Stenzl A, Colleselli K, Bartsch G: Update of urethra-sparing approaches in cystectomy in women. World J Urol. 1997; 15: 134-8.
28. Sanderson KM, Cai J, Miranda G, Skinner DG, Stein JP: Upper tract urothelial recurrence following radical cystectomy for transitional cell carcinoma of the bladder: an analysis of 1,069 patients with 10-year followup. J Urol. 2007; 177: 2088-94.
29. Stenzl A, Bartsch G, Rogatsch H: The remnant urothelium after reconstructive bladder surgery. Eur Urol. 2002; 41: 124-31.
30. Strasser H, Ninkovic M, Hess M, Bartsch G, Stenzl A: Anatomic and functional studies of the male and female urethral sphincter. World J Urol. 2000; 18: 324-9.
31. Kessler TM, Burkhard FC, Perimenis P, Danuser H, Thalmann GN, Hochreiter WW, et al.: Attempted nerve sparing surgery and age have a significant effect on urinary continence and erectile function after radical cystoprostatectomy and ileal orthotopic bladder substitution. J Urol. 2004; 172: 1323-7.
32. Stenzl A, Jarolim L, Coloby P, Golia S, Bartsch G, Babjuk M, et al.: Urethra-sparing cystectomy and orthotopic urinary diversion in women with malignant pelvic tumors. Cancer. 2001; 92: 1864-71.
33. Gburek BM, Lieber MM, Blute ML: Comparison of studer ileal neobladder and ileal conduit urinary diversion with respect to perioperative outcome and late complications. J Urol. 1998; 160: 721-3.
34. Steven K, Poulsen AL: The orthotopic Kock ileal neobladder: functional results, urodynamic features, complications and survival in 166 men. J Urol. 2000; 164: 288-95.
35. Ghoneim MA, Shaaban AA, Mahran MR, Kock NG: Further experience with the urethral Kock pouch. J Urol. 1992; 147: 361-5.
36. Strasser H, Marksteiner R, Margreiter E, Pinggera GM, Mitterberger M, Frauscher F, et al.: Autologous myoblasts and fibroblasts versus collagen for treatment of stress urinary incontinence in women: a randomised controlled trial. Lancet. 2007; 369: 2179-86. Erratum in: Lancet. 2008; 371: 474. Retraction in: Kleinert S, Horton R. Lancet. 2008; 372: 789-90.
37. Strasser H, Tiefenthaler M, Steinlechner M, Bartsch G, Konwalinka G: Urinary incontinence in the elderly and age-dependent apoptosis of rhabdosphincter cells. Lancet. 1999; 354: 918-9.
38. Stenzl A, Colleselli K, Poisel S, Feichtinger H, Pontasch H, Bartsch G: Rationale and technique of nerve sparing radical cystectomy before an orthotopic neobladder procedure in women. J Urol. 1995; 154: 2044-9.

39. Turner WH, Danuser H, Moehrle K, Studer UE: The effect of nerve sparing cystectomy technique on postoperative continence after orthotopic bladder substitution. J Urol. 1997; 158: 2118-22.
40. Abol-Enein H, Ghoneim MA: Functional results of orthotopic ileal neobladder with serous-lined extramural ureteral reimplantation: experience with 450 patients. J Urol. 2001; 165: 1427-32.
41. Wu SD, Simma-Chang V, Stein JP: Pathologic guidelines for orthotopic urinary diversion in women with bladder cancer: a review of the literature. Rev Urol. 2006; 8: 54-60.
42. Ali-el-Dein B, Abdel-Latif M, Ashamallah A, Abdel-Rahim M, Ghoneim M: Local urethral recurrence after radical cystectomy and orthotopic bladder substitution in women: a prospective study. J Urol. 2004; 171: 275-8.
43. Akkad T, Gozzi C, Deibl M, Müller T, Pelzer AE, Pinggera GM, et al.: Tumor recurrence in the remnant urothelium of females undergoing radical cystectomy for transitional cell carcinoma of the bladder: long-term results from a single center. J Urol. 2006; 175: 1268-71; discussion 1271.
44. Ali-El-Dein B, Gomha M, Ghoneim MA: Critical evaluation of the problem of chronic urinary retention after orthotopic bladder substitution in women. J Urol. 2002; 168: 587-92.
45. Stein JP, Stenzl A, Grossfeld GD, Freeman JA, Esrig D, Boyd SD, et al.: The use of orthotopic neobladders in women undergoing cystectomy for pelvic malignancy. World J Urol. 1996; 14: 9-14.
46. Hautmann RE: The ileal neobladder to the female urethra. Urol Clin North Am. 1997; 24: 827-35.
47. Bhatta Dhar N, Kessler TM, Mills RD, Burkhard F, Studer UE: Nerve-sparing radical cystectomy and orthotopic bladder replacement in female patients. Eur Urol. 2007; 52: 1006-14.
48. Thüroff JW, Franzaring L, Gillitzer R, Wöhr M, Melchior S: Simplified orthotopic ileocaecal pouch (Mainz pouch) for bladder substitution. BJU Int. 2005; 96: 443-65.
49. Okada H, Yamanaka N, Oh-Oka H, Gotoh A, Nakamura I, Hara I, et al.: Construction and voiding functions of three types of orthotopic neobladders using colonic segments: the Kobe University experience. Int J Urol. 1998; 5: 22-9.
50. Schrier BP, Laguna MP, van der Pal F, Isorna S, Witjes JA: Comparison of orthotopic sigmoid and ileal neobladders: continence and urodynamic parameters. Eur Urol. 2005; 47: 679-85.
51. Kouba E, Sands M, Lentz A, Wallen E, Pruthi RS: A comparison of the Bricker versus Wallace ureteroileal anastomosis in patients undergoing urinary diversion for bladder cancer. J Urol. 2007; 178: 945-8; discussion 948-9.
52. Stenzl A, Hobisch A, Strasser H, Bartsch G: Ureteroileal anastomosis in orthotopic urinary diversion: how much or how little is necessary? Tech Urol. 2001; 7: 188-95.
53. Henningsohn L, Steven K, Kallestrup EB, Steineck G: Distressful symptoms and well-being after radical cystectomy and orthotopic bladder substitution compared with a matched control population. J Urol. 2002; 168: 168-74; discussion 174-5.
54. Hobisch A, Tosun K, Kinzl J, Kemmler G, Bartsch G, Höltl L, et al.: Quality of life after cystectomy and orthotopic neobladder versus ileal conduit urinary diversion. World J Urol. 2000; 18: 338-44.
55. Hart S, Skinner EC, Meyerowitz BE, Boyd S, Lieskovsky G, Skinner DG: Quality of life after radical cystectomy for bladder cancer in patients with an ileal conduit, cutaneous or urethral kock pouch. J Urol. 1999; 162: 77-81.
56. Allareddy V, Kennedy J, West MM, Konety BR: Quality of life in long-term survivors of bladder cancer. Cancer. 2006; 106: 2355-62.
57. Gerharz EW, Månsson A, Hunt S, Skinner EC, Månsson W: Quality of life after cystectomy and urinary diversion: an evidence based analysis. J Urol. 2005; 174: 1729-36.
58. Schoenberg MP, Walsh PC, Breazeale DR, Marshall FF, Mostwin JL, Brendler CB: Local recurrence and survival following nerve sparing radical cystoprostatectomy for bladder cancer: 10-year followup. J Urol. 1996; 155: 490-4.
59. Miyao N, Adachi H, Sato Y, Horita H, Takahashi A, Masumori N, et al.: Recovery of sexual function after nerve-sparing radical prostatectomy or cystectomy. Int J Urol. 2001; 8: 158-64.
60. Volkmer BG, Gschwend JE, Herkommer K, Simon J, Küfer R, Hautmann RE: Cystectomy and orthotopic ileal neobladder: the impact on female sexuality. J Urol. 2004; 172: 2353-7.
61. Zippe CD, Raina R, Shah AD, Massanyi EZ, Agarwal A, Ulchaker J, et al.: Female sexual dysfunction after radical cystectomy: a new outcome measure. Urology. 2004; 63: 1153-7.
62. Nandipati KC, Bhat A, Zippe CD: Neurovascular preservation in female orthotopic radical cystectomy significantly improves sexual function. Urology. 2006; 67: 185-6.
63. Mills RD, Studer UE: Metabolic consequences of continent urinary diversion. J Urol. 1999; 161: 1057-66.

64. Hautmann RE: Urinary diversion: ileal conduit to neobladder. J Urol. 2003; 169: 834-42.
65. Gschwend JE, Hautmann RE, Volkmer BG: Radical cystectomy and urinary diversion in elderly patients with increased comorbidity. Urologe A. 2004; 43: 930-4.
66. Clark PE, Stein JP, Groshen SG, Cai J, Miranda G, Lieskovsky G, et al.: Radical cystectomy in the elderly: comparison of clincal outcomes between younger and older patients. Cancer. 2005; 104: 36-43.
67. Figueroa AJ, Stein JP, Dickinson M, Skinner EC, Thangathurai D, Mikhail MS, et al.: Radical cystectomy for elderly patients with bladder carcinoma: an updated experience with 404 patients. Cancer. 1998; 83: 141-7.

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Complications Rates of Non-Oncologic Urologic Procedures in Population-based Data: A Comparison to Published Series

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ABSTRACT

Purpose: Published single institutional case series are often performed by one or more surgeons with considerable expertise in specific procedures. The reported incidence of complications in these series may not accurately reflect community-based practice. We sought to compare complication and mortality rates following urologic procedures derived from population-based data to those of published single-institutional case series.

Materials and Methods: In-hospital mortality and complications of common urologic procedures (percutaneous nephrostomy, ureteropelvic junction obstruction repair, ureteroneocystostomy, urethral repair, artificial urethral sphincter implantation, urethral suspension, transurethral resection of the prostate, and penile prosthesis implantation) reported in the U.S.'s National Inpatient Sample of the Healthcare Cost and Utilization Project were identified. Rates were then compared to those of published single-institution series using statistical analysis.

Results: For 7 of the 8 procedures examined, there was no significant difference in rates of complication or mortality between published studies and our population-based data. However, for percutaneous nephrostomy, two published single-center series had significantly lower mortality rates ($p < 0.001$). The overall rate of complications in the population-based data was higher than published single or select multi-institutional data for percutaneous nephrostomy performed for urinary obstruction ($p < 0.001$).

Conclusions: If one assumes that administrative data does not suffer from under reporting of complications then for some common urological procedures, complication rates between population-based data and published case series seem comparable. Endorsement of mandatory collection of clinical outcomes is likely the best way to appropriately counsel patients about the risks of these common urologic procedures.

Key words: *urology; complications, urologic procedures, informed consent*
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INTRODUCTION

Much of the knowledge regarding expected post procedural complications and rates of such complications is derived from reports of case series from single institutions or a small group of institutions. Practicing urologists generally use these rates of surgical complications and mortality in counseling patients prior to a surgical procedure. However, the reported incidence of complications in such exclusive case series may or may not reflect those of community practitioners.

There is growing interest in standardizing the process of informed consent in regards to what

aspects are discussed and the probabilities of certain outcomes (1). In fact, the British Department of Health had previously issued a model consent form in 2002 for use throughout the National Health System (NHS) to address this matter. In addition, the American College of Surgeons (ACS) has released a Professional Code of Conduct in which section II. A describes the duty of obtaining informed consent to "include the estimated risks of mortality and morbidity" (2). Yet, it is probable that rates of complication or mortality during a given procedure may vary based on institution and provider.

It is unclear if complication rates from single or small groups of institutions are reflective of that observed in the community at large. One study did not find a difference between the complication rates of tertiary care centers and population-based data for radical cystectomy (3). Clearly, a system where physicians report their own complication rates would be the most accurate way of gaining informed consent. However, there is yet little incentive to collect this data by single physicians or institutions, as it is costly and labor intensive. We therefore sought to compare in-patient complication and mortality rates derived from population-based data obtained from a national data source to those from contemporary published single-institution case series for common urologic procedures.

MATERIALS AND METHODS

Study Design

We performed a retrospective analysis of the Nationwide Inpatient Sample (NIS) of the Health Care Utilization Project for 2000 to 2004. Briefly, the NIS is a 20% stratified sample of all community hospitals in the United States and contains 5 to 8 million records from approximately 1000 hospitals in 35 states (4). We used this national dataset to explore rates of complications and mortality following a selection of commonly performed urologic procedures and compared these rates to reported series in the literature.

Patient Population

We identified all patients with a primary urologic procedure noted for a single admission, excluding those procedures performed for malignancy (radical prostatectomy and radical nephrectomy). These were identified by using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) system (5). A list consisting of 8 groups of like procedures was constructed which excluded procedures done for malignancy (Table-1).

Outcomes

The primary outcome was in-patient rate of complication, group coded in the NIS using the clinical classification software (CCS) coding system (code 238; "complications of surgical procedures or medical care") and found under the category of secondary diagnosis (6). Our secondary outcome was a diagnosis of death (in hospital mortality).

Literature Search

Using PubMED we performed a literature search for large, contemporary (arbitrarily defined as published after 1995), and single-institutional case series for each of our 8 procedural groups examined. We further restricted our search to articles that included data on complication rates and were published in English-language journals. From these publications, we extracted complication rates and mortality. We excluded data from older literature as significant changes in the technology and practice of urology that have occurred since that time may make it hard to compare current practice realities to a time period older that that. We also wanted to ensure that we were utilizing reports from the immediate 5 year time period prior to our period of analysis (2000-2004) in order to ensure that any new procedures or technologies that had been used in published reports had sufficient time to become incorporated into routine practice. Keywords used for the literature search were complication rate, procedure name (nephrostomy, urethral sling/suspension, penile prosthesis, artificial urinary sphincter, transurethral prostatectomy), and mortality.

Table 1 *– Procedure definitions and corresponding ICD-9 codes.*

Procedure (N)	**ICD-9 Code**	**Description**
Procedure 1 (26263)	55.03	percutaneous nephrostomy without stone fragmentation
	55.04	percutaneous nephrostomy with stone fragmentation
Procedure 3 (5074)	55.87	correct ureteropelvic junction obstruction
Procedure 4 (7464)	56.74	ureteroneocystostomy
Procedure 5 (2404)	58.44	urethral reanastamosis
	58.45	hypo-epispadias repair
	58.46	urethral reconstruction nec
	58.49	urethral repair nec
Procedure 6 (1875)	58.93	implant artificial urinary sphincter
Procedure 7 (39737)	59.4	suprapubic sling
	59.5	retropubic urethral suspension
	59.6	paraurethral suspension
	59.71	levator muscle suspension
	59.79	urinary incontinence repair nec
Procedure 8 (117025)	60.21	transurethral prostatectomy
	60.29	other transurethral prostatectomy
	60.3	suprapubic prostatectomy
	60.4	retropubic prostatectomy
Procedure 10 (6225)	64.95	insert non-inflatable penile prosthesis
	64.96	remove internal penile prosthesis
	64.97	insert inflatable penile prosthesis

**Procedures 2 and 9 were radical nephrectomy and radical prostatectomy, respectively. Procedures performed for malignancy were excluded from this study. ICD = International Classification of Diseases.*

Statistical Analysis

For each procedure, the in-hospital complication rate from the HCUP dataset was compared to the rates from the publications identified in our literature search using Pearson's chi-square analysis. Mortality rates were compared using Fisher's exact test. All analyses were performed using STATA version 9.2 (Stata Corp., College Station, TX), and a two-tailed p-value < 0.05 was considered significant.

RESULTS

Our literature search found 14 large contemporary published series that included complication statistics for 10 different procedures spanning all 8 of our procedure categories. The publications for each procedure are included in Table-2, along with the corresponding publication date, number of patients, and patient accrual period, when available (7-20).

For 7 of the 8 procedures examined, there was no significant difference in complication rates or mortality between published studies and our population-based data (Table-3). For percutaneous nephrostomy, two published single-center series had significantly lower mortality rates than the population-based data set (0.31% and 0.32% vs. 2.7%, $p < 0.001$). The overall rate of complications in the population-based data was higher than published data for percutaneous nephrostomy performed for urinary obstruction (10.0% vs. 3.4%, $p < 0.001$), but similar to

Table 2 – *List of case series from our literature search.*

Procedure Category	First Author	Procedure Performed	N. Patients	Date of Publication	Accrual Period
1	Skolarikos (4)	percutaneous nephrostomy for obstruction	650	2006	1996-2005
	Osman (5)	percutaneous nephrostomy with nephrolithotomy	315	2005	1987-2002
3	Moon (6)	laparoscopic pyeloplasty	170	2006	UNK
	Jarrett (7)	laparoscopic pyeloplasty	100	2002	1993-1999
4	Duong (8)	ureteroneocystostomy	300	2003	1996-2002
5	Perlmutter (9)	hypospadias repair	316	2006	1999-2005
	Fu (10)	hypospadias repair	294	2006	1993-2003
	Hammouda (11)	epispadias repair	42	2003	1998-2002
6	Costa (12)	implantation of AUS	207	2001	1989-1998
7	Levin (13)	tension-free vaginal tape	331	2004	UNK
	Hodroff (14)	SPARC	445	2005	2001-2003
8	Borboroglu (15)	TURP	520	1999	1991-1998
10	Minervini (16)	implant penile prosthesis (both malleable and inflatable)	482	2005	1975-2000
	Chiang (17)	implant penile prosthesis (various types)	331	2000	1985-1996

AUS = artificial urinary sphincter; SPARC = supra-pubic arc sling; TURP = transurethral resection of the prostate, UNK = unknown.

the rate observed when nephrostomy was performed with percutaneous nephrolithotomy (10.1%) (8,9).

COMMENTS

The absence of a nationalized system (as seen in England and Canada) for reporting a surgeon's post-operative complications may impede the patient's ability to give informed consent. Currently, most physicians provide rates of complication and mortality for a given procedure, by citing single institutional case series oftentimes published by high-volume surgeons. We sought to examine the complication and mortality rates during various urologic procedures for the treatment of benign disease in a nationally (for the U.S.) collected dataset called the Nationwide Inpatient sample (NIS) collected by the Healthcare Cost and Utilization Project (HCUP) from 2000 to 2004. In addition, we hoped to compare these rates to those reported by single institutional series to address the question of whether the later are adequate for the use in gaining informed consent from patients. We found in this study, that for select urologic procedures, point estimates of complication and mortality discovered using population-based datasets were nearly comparable to those reported from single or groups of institutions. A prior report showed a similar finding for complication rates of radical cystectomy (3).

The finding of a higher rate of complication and mortality for patients undergoing nephrostomy in the population-based national dataset when compared to the cited single institutional series also deserves further scrutiny (8,9). A breakdown of group 1 by the two ICD-9-CM codes contained within it

Table 3 – *Comparisons of complication rates and mortality rates between HCUP data set and published single-institution case series.*

Procedure	Study	N	Complications (%)	p Value*	Mortality (%)	p Value†
Percutaneous nephrostomy				< 0.001		< 0.001
	HCUP	26263	2621 (10.00)		716 (2.73)	
	Skolarikos, et al.	650	22 (3.38)		2 (0.31)	
	Osman, et al.	315	32 (10.16)		1 (0.32)	
Pyeloplasty				0.16		0.90
	HCUP	5074	400 (7.88)		4 (0.08)	
	Moon, et al.	170	12 (7.06)		0	
	Jarrett, et al.	100	13 (13.00)		0	
Ureteroneocystostomy				0.98		1.00
	HCUP	7464	749 (10.03)		4 (0.05)	
	Duong, et al.	300	30 (10.00)		0	
Urethral repair				0.15†		1.00
	HCUP	2404	152 (6.32)		3 (0.12)	
	Perlmutter, et al.	316	25 (7.91)		0	
	Fu, et al.	294	27 (9.18)		0	
	Hammouda, et al.	42	1 (2.38)		0	
Artificial urinary sphincter				0.52		1.00
	HCUP	1875	407 (21.71)		5 (0.27)	
	Costa, et al.	207	49 (23.67)		0	
Urethral resuspension				0.65		1.00
	HCUP	39737	2747 (6.91)		10 (0.03)	
	Levin, et al.	331	20 (6.04)		0	
	Hodroff, et al.	445	27 (6.07)		0	
Transurethral resection of prostate				0.95		0.42
	HCUP	117025	7126 (6.09)		358 (0.31)	
	Borboroglu, et al.	520	32 (6.15)		0	
Penile prosthesis				0.23		1.00
	HCUP	6225	616 (9.90)		8 (0.13)	
	Minervini, et al.	482	37 (7.68)		0	
	Chiang, et al.	331	36 (10.88)		0	

** p value by chi-square test except where noted; † p value by Fisher's exact test; HCUP = Healthcare Cost and Utilization Project.*

demonstrated that 5,945 (23%) patients underwent percutaneous nephrolithotomy (PNL) for treatment of nephrolithiasis and 20,318 (77%) patients underwent simple nephrostomy tube placement for renal obstruction. One explanation for the higher complication rate found in the population-based data for those undergoing nephrostomy (including PNL) compared to our cited case series could be related to

the heterogeneity of patients and procedures within group 1. Despite our desire to exclude patients with malignancy in this study (by excluding procedures performed for malignancy), it is conceivable that some individuals at the national level were given percutaneous nephrostomies to treat malignant renal obstruction. Presumably then this cohort would be sicker than those included in our case series would. Another explanation may have to do with the type of physicians placing the nephrostomy tube. The case series report data collected on patients treated only by urologists whereas our nationally representative sample likely contains patients treated by Interventional Radiologists as well.

It is important to note this study's other limitations. ICD-coding may inaccurately identify surgical complications (21-23). One must assume that single institutional data derived from direct chart abstraction is more comprehensive. However, chart review is subject to interpretation and selection bias on the part of the abstractors while claims data are not restrictive in this sense. In addition, we report only inpatient events as we are limited to this time frame by our dataset, but some complications occur after discharge.

Another limitation of this study is that we were unable to risk stratify patients by disease severity, age, gender, etc. The patients in the NIS might vary in these characteristics dramatically when compared to single institutional studies. However, tertiary centers responsible for the cited case series typically would treat sicker patients and thereby any bias would be expected to result in higher, not lower, rates of complications and mortality.

The selection of case series to compare to the data collected for this analysis is admittedly inexact. We attempted to select publications that were large, representative and would provide meaningful information from large institutional observational studies. However, it is possible that there are selection biases in terms of studies that are published and the comprehensiveness of our literature search itself. In addition, it is possible that some of the patients in these case series are also found in the NIS, though this number is likely quite small. Nevertheless, we feel that the selected studies provide a representative comparator.

CONCLUSIONS

In conclusion, for some common urological procedures, complication rates between population-based data and published case series seem comparable if one were to completely discount underreporting of complications in administrative datasets. We do not, however, suggest that these data be interpreted as a justification for replacing self-collection of outcomes. Given the current health care climate in the U.S. and movements towards transparency, it is likely one day that provider-level data on morbidity and mortality will become available to better assist patients and physicians with healthcare decision-making. This is already underway in other countries and beginning to roll out in the U.S. through the comprehensive surgical registry, National Surgical Quality Improvement Project, supported by the American College of Surgeons.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Berman L, Dardik A, Bradley EH, Gusberg RJ, Fraenkel L: Informed consent for abdominal aortic aneurysm repair: assessing variations in surgeon opinion through a national survey. J Vasc Surg. 2008; 47: 287-295.
2. American College of Surgeon´s Code of Professional Conduct. 2003 [cited 20 March]; Available from: http://www.facs.org/fellows_info/statements/stonprin.html#anchor116209
3. Konety BR, Allareddy V, Herr H: Complications after radical cystectomy: analysis of population-based data. Urology. 2006; 68: 58-64.
4. Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality. Available online at URL: http://www.ahrq.gov/data/hcup/ (accessed February 9).
5. 1999 Hospital & payor ICD-9-CM: international classification of diseases tr, clinical modification. 5th ed. Salt Lake City, Medicode, 1998.
6. HCUP: 2004 [cited 2004 January 13th]; Available from: http://www.hcup-us.ahrq.gov/toolssoftware/ccs/AppendixASingleDX.txt

7. Fu Q, Deng CL: Ten-year experience with composite bladder mucosa-skin grafts in hypospadias repair. Urology. 2006; 67: 1274-7; discussion 1277.
8. Skolarikos A, Alivizatos G, Papatsoris A, Constantinides K, Zerbas A, Deliveliotis C: Ultrasound-guided percutaneous nephrostomy performed by urologists: 10-year experience. Urology. 2006; 68: 495-9.
9. Osman M, Wendt-Nordahl G, Heger K, Michel MS, Alken P, Knoll T: Percutaneous nephrolithotomy with ultrasonography-guided renal access: experience from over 300 cases. BJU Int. 2005; 96: 875-8.
10. Jarrett TW, Chan DY, Charambura TC, Fugita O, Kavoussi LR: Laparoscopic pyeloplasty: the first 100 cases. J Urol. 2002; 167: 1253-6.
11. Moon DA, El-Shazly MA, Chang CM, Gianduzzo TR, Eden CG: Laparoscopic pyeloplasty: evolution of a new gold standard. Urology. 2006; 67: 932-6.
12. Duong DT, Parekh DJ, Pope JC 4th, Adams MC, Brock JW 3rd: Ureteroneocystostomy without urethral catheterization shortens hospital stay without compromising postoperative success. J Urol. 2003; 170: 1570-3; discussion 1573.
13. Perlmutter AE, Morabito R, Tarry WF: Impact of patient age on distal hypospadias repair: a surgical perspective. Urology. 2006; 68: 648-51.
14. Hammouda HM: Results of complete penile disassembly for epispadias repair in 42 patients. J Urol. 2003; 170: 1963-5; discussion 1965.
15. Costa P, Mottet N, Rabut B, Thuret R, Ben Naoum K, Wagner L: The use of an artificial urinary sphincter in women with type III incontinence and a negative Marshall test. J Urol. 2001; 165: 1172-6.
16. Levin I, Groutz A, Gold R, Pauzner D, Lessing JB, Gordon D: Surgical complications and medium-term outcome results of tension-free vaginal tape: a prospective study of 313 consecutive patients. Neurourol Urodyn. 2004; 23: 7-9.
17. Hodroff MA, Sutherland SE, Kesha JB, Siegel SW: Treatment of stress incontinence with the SPARC sling: intraoperative and early complications of 445 patients. Urology. 2005; 66: 760-2.
18. Borboroglu PG, Kane CJ, Ward JF, Roberts JL, Sands JP: Immediate and postoperative complications of transurethral prostatectomy in the 1990s. J Urol. 1999; 162: 1307-10.
19. Minervini A, Ralph DJ, Pryor JP: Outcome of penile prosthesis implantation for treating erectile dysfunction: experience with 504 procedures. BJU Int. 2006; 97: 129-33.
20. Chiang HS, Wu CC, Wen TC: 10 years of experience with penile prosthesis implantation in Taiwanese patients. J Urol. 2000; 163: 476-80.
21. McCarthy EP, Iezzoni LI, Davis RB, Palmer RH, Cahalane M, Hamel MB, et al.: Does clinical evidence support ICD-9-CM diagnosis coding of complications? Med Care. 2000; 38: 868-76.
22. Weingart SN, Iezzoni LI, Davis RB, Palmer RH, Cahalane M, Hamel MB, et al.: Use of administrative data to find substandard care: validation of the complications screening program. Med Care. 2000; 38: 796-806.
23. Lawthers AG, McCarthy EP, Davis RB, Peterson LE, Palmer RH, Iezzoni LI: Identification of in-hospital complications from claims data. Is it valid? Med Care. 2000; 38: 785-95.

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EDITORIAL COMMENT

In this article by Aaronson et al., the authors compare the morbidity and mortality rates of non-oncologic common urological procedures between national population-based data and single-institution published series. Except for percutaneous nephrostomy (PN), the remainder procedures (ureteropelvic junction obstruction repair, ureteroneocystostomy, urethra repair, artificial urethra sphincter implantation, urethral suspension, transurethral resection of the prostate, penile prosthesis implantation) shared comparable rates between the two study groups. This conclusion is useful in the absence of a nationalized system for reporting a surgeon's complications and helps the patient to give informed consent.

Similar studies are encouraged in order to confirm if other urological procedures have comparable data or if there are statistically significant differences such as in the case of PN (this could be attributed to the availability of relevant recourses). Konety et al., demonstrated that morbidity and mortality rates after radical cystectomy in a population-based sample were comparable to those reported from individual centers (1). They found that larger centers in urban locations may have lower complication rates but only hospitals performing a high volume of cystectomies were associated with fewer primary surgery-related complications.

Except for registering all complications, surgeons are encouraged to classify their complications in each urological procedure. In the literature there are several standardized classification systems for reporting surgical complications (2,3). The incorporation of such classification systems will help colleagues and patients to assess better and compare the risks of each operation.

In the future, provider-level data on morbidity and mortality should become available in favor of healthcare decision-making. Online registration by every urological surgeon (within hospitals, national and/or international associations) of the morbidity and mortality data for all standard urological procedures should be organized as this will meet relevant patient's expectations.

REFERENCES

1. Konety BR, Allareddy V, Herr H. Complications after radical cystectomy: analysis of population-based data. Urology. 2006; 68: 58-64.
2. Martin RC 2nd, Brennan MF, Jaques DP: Quality of complication reporting in the surgical literature. Ann Surg. 2002; 235: 803-13.
3. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al.: The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009; 250: 187-96.

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EDITORIAL COMMENT

In this data comparison, the authors tried to establish whether it is reasonable in a general urology practice to counsel patients on perioperative complications of selected urological procedures, based on figures from large, single institution published series. The study has a number of shortcomings (highlighted

by the authors), of which the most obvious is the difficulty in extrapolating useful and practical information from a database like the Healthcare Cost and Utilization Project. One can only speculate as to why the complication rate for percutaneous nephrostomies was higher in the population-based dataset, and probably reflects the lack of stratification of the reason for renal obstruction (e.g. advanced stage malignancy). The article does highlight the importance of accurate surgical audits (on institutional and national levels) to improve surgical outcomes and aid in the preoperative counseling of patients.

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Urinary Lithiasis and Idiopathic Hypercalciuria: The Importance of Dietary Intake Evaluation

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ABSTRACT

*Purpose: T*o evaluate food intake of patients with urinary lithiasis and idiopathic hypercalciuria (IH).
Materials and Methods: Between August 2007 and June 2008, 105 patients with lithiasis were distributed into 2 groups: Group 1 (n = 55) - patients with IH (urinary calcium excretion > 250 mg in women and 300 mg in men with normal serum calcium); Group 2 (n = 50) – normocalciuria (NC) patients . Inclusion criteria were: age over 18, normal renal function (creatinine clearance ≥ 60 mL/min), absent proteinuria and negative urinary culture. Pregnant women, patients with some intestinal pathology, chronic diarrhea or using corticoids were excluded. The protocol of metabolic investigation was based on non-consecutive collection of two 24-hour samples for dosages of: calcium, sodium, uric acid, citrate, oxalate, magnesium and urinary volume. Food intake was evaluated through the quantitative method of Dietary Register of three days.
Results: Urinary excretion of calcium (433.33 ± 141.92 vs. 188.93 ± 53.09), sodium (280.08 ± 100.94 vs. 200.44.93 ± 65.81), uric acid (880.63 ± 281.50 vs. 646.74 ± 182.76) and magnesium (88.78 ± 37.53 vs. 64.34 ± 31.84) was significantly higher in the IH group in comparison to the NC group ($p < 0.05$). As regards the nutritional composition of food intake of IH and NC groups, there was no statistical significant difference in any nutrient evaluated.
Conclusion: In our study, no difference was observed in the food intake of patients with urinary lithiasis and IH or NC.

Key words: *lithiasis; hypercalciuria; metabolic evaluation; food intake*
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INTRODUCTION

Urinary lithiasis has multifactorial causes, depending on different factors such as hereditariness, climate, anatomic alterations and urinary tract infection, metabolic disorders and food intake (1).

Nearly 95% of patients with lithiasis present metabolic alterations (2), and, in Brazil, this prevalence may range 93-97% of cases (3,4). Some of the metabolic causes of stones are hypercalciuria, hypocitraturia, gouty diathesis, hyperoxaluria and hyperuricosuria (5). Idiopathic hypercalciuria (IH) is the most frequently detected metabolic disorder, varying according to the evaluated region (3,6). It is defined by elevated urinary excretion of calcium, in the presence of normocalcemia (7).

Among the environmental factors, food intake is highly important to prevent urinary lithiasis recurrence. This way, the role of some dietary nutrients, mainly calcium, protein and sodium, have been

recently investigated for their likely effects as either promoters or inhibitors of calculus formation (8).

This study aims to evaluate food intake of patients with urinary lithiasis and IH.

MATERIALS AND METHODS

Between August 2007 and June 2008, 105 patients with lithiasis were prospectively studied at the Outpatient Clinic of Metabolism in Renal Lithiasis of the Clinical Hospital of Botucatu. This study was approved by the Bioethics Commission of the School of Medicine - UNESP, Botucatu.

Inclusion criteria were: age over 18 years, normal renal function (creatinine clearance ≥ 60 mL/min), absence of proteinuria and negative uroculture at the moment of evaluation. Pregnant women, patients with any intestinal pathology (chronic diarrhea or Crohn's Disease), calcium metabolism disorders (primary hyperparathyroidism, hyperthyroidism, osteoporosis) or patients who used corticoids were excluded.

The metabolic investigation protocol consisted of non-consecutive collection of two samples of 24-hour urine for dosages of calcium, sodium, uric acid, citrate, oxalate, magnesium and urinary volume. Serum dosage of calcium, phosphorus, uric acid, sodium and parathormone was performed in all patients.

The patients were distributed into two groups. IH was considered the urinary excretion of calcium > 250 mg for women and 300 mg for men with normal serum calcium. Group 1 (n = 55) – consisted of patients with IH; Group 2 (n = 50) - Normocalciuric (NC), were considered as patients with normal urinary excretion of calcium.

Food intake was evaluated through the quantitative method of 3-day food record (9). One day on the weekend and two non-consecutive weekdays were fixed (10). The NutWin (2002) - Program of Nutrition Support of Paulista School of Medicine of the Federal University of Sao Paulo was used to calculate the total daily consumption of calories, carbohydrates, lipids, total protein, animal protein and calcium of the patients during the 3-day food record. Sodium (Na) excreted in the 24-hour urine was used as a marker of the daily sodium consumption (11).

Body Mass Index (BMI) was calculated and classified according to World Health Organization (WHO) (12).

Student's-t parametric test was used for independent samples to compare the groups of patients with calcium and non-calcium urinary lithiasis in relation to the quantitative variables studied when the variable presented adherence to Gaussian distribution; and the Wilcoxon-Mann Whitney non-parametric test was used in cases of non-adherence. Considering the study of the association between pairs of variables, Pearson's linear correlation was used (13). Differences were considered significant for p value < 0.05.

RESULTS

Among the 105 patients studied, there was homogeneous distribution in both groups as regards mean age, weight, height and BMI (Body Mass Index) (Table-1). However, it was observed that, in average, according to BMI, patients in both groups were overweighed.

Among the IH patients, there were 60% of women in a proportion to men of 1.5:1, and 56% in a proportion of 1.27:1 in the NC group. There was no statistically significant difference between the groups (p > 0.05).

In the IH groups, the 24-hour urine volume was between 1,000 and 2,000 mL and in 9% higher than 2,000 mL. As for the NC group, 78% was between 1,000 and 2,000 mL, and 4% higher than 2,000 mL. There was no significant difference between the groups (p > 0.05).

The mean urinary excretion of calcium, sodium, uric acid and magnesium was significantly higher in the IH group than in the NC group (Table-2).

As for the nutritional composition of food intake, there was no statistically difference in the average evaluated nutrients in none of the groups (Table-3).

On average, the protein intake was similar in both groups (Table-3).

Table 1 – *Demographics characteristics of the different studied groups.*

	Group		Statistical Analysis
	IH (N = 55)	**NC** (N = 50)	
Age (years)	42.11 ± 10.61	46.14 ± 11.52	p > 0.05
Weight (kg)	77.14 ± 16.03	75.99 ± 15.80	p > 0.05
Height (meters)	1.64 ± 0.10	1.64 ± 0.08	p > 0.05
BMI (kg/m²)	28.78 ± 5.81	28.07 ± 5.27	p > 0.05
Volume (mL/24h)	1433.55 ± 474.81	1314.40 ± 392.39	p > 0.05

BMI = body mass index; IH = Idiopathic hypercalciuria; NC = Normocalciuric.

COMMENTS

Overweight was observed in both groups. These data corroborate other authors (12,14), who demonstrated increased incidence of lithiasis in obese and overweighed patients of both genders.

Epidemiologic studies showed higher prevalence of the lithiasis in male patients (15), however, until now there has been no explanation for this predominance. A transversal analysis in this study showed higher predominance in women in both groups. Other similar studies do not show remarkable differences as for gender (16). These findings can be justified by the higher level of commitment of women in the outpatient follow-up, without reflecting the general gender prevalence in relation to the population with lithiasis.

The risk of calculus formation decreases when the urinary volume is higher than 2,000 mL and low volume may be considered a risk factor as well as a metabolic disorder for lithiasis (17). This series observed higher predominance of urinary volume between 1,000 and 2,000 mL in both groups; there was no interference of this parameter. There was no statistically significant difference between the groups.

High intake of sodium decreases the renal absorbency of calcium leading to increased calciuria (17,18), therefore it can be inferred that sodium plays an important role in the genesis of lithiasis.

The excretion of uric acid was significantly higher in the IH group which can be explained by the high prevalence of mixed metabolic alterations in our series and their relation to the elevated animal protein intake observed.

Urinary excretion of magnesium was significantly higher in the IH group. Similar data have been described by other authors (18), who reported

Table 2 – *Description of median and standard deviation of biochemical characteristics of 24-hour urine in the different studied groups.*

Urinary Excretion	Group		Statistical Analysis
	IH (N = 55)	**NC** (N = 50)	
Calcium (mg/24h)	433.33 ± 141.92	188.93 ± 53.09	p < 0.05
Sodium (mEq/24h)	280.08 ± 100.94	200.44 ± 65.81	p < 0.05
Uric acid (mg/24h)	880.63 ± 281.50	646.74 ± 182.76	p < 0.05
Magnesium (mg/24h)	88.78 ± 37.53	64.34 ± 31.84	p < 0.05
Citrate (mg/24h)	563.64 ± 505.45	454.89 ± 361.98	p > 0.05
Oxalate (mg/24h)	34.57 ± 23.41	42.40 ± 28.10	p > 0.05

IH = Idiopathic hypercalciuria; NC = Normocalciuric.

Table 3 – *Description of median and standard deviation of the composition of daily food intake in the different studied groups.*

Nutrient	Group		Statistical Analysis
	IH (N = 55)	**NC** (N = 50)	
Energy (kcal)	2046.70 ± 1405.42	1791.62 ± 536.03	p > 0.05
Proteins (g)	81.78 ± 37.65	82.06 ± 29.27	p > 0.05
Protein (g/kg weight/day)	1.10 ± 0.47	1.10 ± 0.40	p > 0.05
Animal protein (%)	64.33 ± 42.01	64.78 ± 29.46	p > 0.05
Carbohydrates (g)	243.10 ± 82.03	227.57 ± 83.70	p > 0.05
Lipids (g)	63.08 ± 26.53	64.22 ± 20.71	p > 0.05
Calcium (mg)	520.13 ± 245.62	531.44 ± 299.48	p > 0.05

IH = Idiopathic hypercalciuria; NC = Normocalciuric.

a directly proportional relation between urinary calcium and magnesium (19). However, studies about the role of magnesium in urinary lithiasis are highly controversial (4,20).

Although there was no difference in the ingestion of different nutrients in the studied groups, the calcium intake was lower than that recommended to patients with lithiasis, which should range between 800 to 1,000 mg of calcium/day (21). This fact is likely due to the patients' belief that low calcium intake could reduce the recurrence of lithiasis. Therefore, in most cases, calcium restriction is not advisable.

Both groups presented daily protein intake higher than that recommended, as well as high mean intake of animal protein, considering that 50% of the maximum total intake should be animal protein. However, milk and its by-products, despite their origin, should not be restricted due to the high amount of calcium (21). Some authors (22) have suggested that the incidence of urinary calculi, mainly the calcium originated, is directly related to the amount of animal protein. It is important to recommend lower intake of animal protein to patients with lithiasis, which will contribute to lower lithiasis recurrence. The clinical treatment offered to these patients with lithiasis must include a dietary modification, as well as drug therapies to identify and correct these metabolic disorders thus reducing the recurrence of this pathology.

In our study, no difference was observed in the food intake of patients with urinary lithiasis and IH or NC.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Heilberg IP, Schor N, Dos Santos DR, Cheidde L, Noronha N, Duarte RJ, et al.: Diretrizes de litíase urinária da sociedade brasileira de nefrologia. J Bras Nefrol. 2002; 24: 2003-7.
2. Levy FL, Adams-Huet B, Pak CY: Ambulatory evaluation of nephrolithiasis: an update of a 1980 protocol. Am J Med. 1995; 98: 50-9.
3. Laranja SMR, Heilberg IP, Coelho STSN, Novoa CG, Schor N: Estudo Multicêntrico de Litíase Renal no Brasil (MULTILIT). In: Schor N, Heilberg IP (ed.), Calculose renal: fisiopatologia, diagnóstico, tratamento. São Paulo, Sarvier. 1995; pp. 295-8.
4. Amaro CR, Amaro JL, Goldberg J: Comportamento do magnésio urinário em pacientes com litíase renal. J Bras Nefrol. 2005; 27: 146-9.
5. Pak CY: Medical management of urinary stone disease. Nephron Clin Pract. 2004; 98: c49-53.
6. Chula DC, Campos RP, Nascimento DE, Carvalho M: Caracterização clínica dos pacientes com hipercalciúria na nefrolitíase. J Bras Nefrol. 2006; 2: 72-6.
7. Hodgkinson A, Pyrah LN: The urinary excretion of calcium and inorganic phosphate in 344 patients with calcium stone of renal origin. Br J Surg. 1958; 46: 10-8.
8. Hess B: Nutritional aspects of stone disease. Endocrinol Metab Clin North Am. 2002; 31: 1017-30.

9. Burke B: The dietary history as a tool in research. J Am Diet Assoc. 1947; 23: 1041-6.
10. Willett WC: Nutritional epidemiology. In: Rothman KJ, Greenland S (ed.), Modern epidemiology. Philadelphia; Lippincott-Raven Publishers. 1998; pp. 623-42.
11. World Health Organization: Reducing Salt intake in populations. Report of a WHO Forum and Technical Meeting" Geneva, World Health Organization [cited 2007 apr 16], 2007. Available at: http://www.who.int/dietphysicalactivity/Salt_Report_VC_april07.pdf
12. World Health Organization: Obesity: preventing and managing the global epidemic. Report of a WHO Consultation. WHO Technical Report Series 894. Geneva: World Health Organization [cited 2008 nov 10], 2000. Available at: http://www.who.int/bmi/index.jsp?introPage=intro_3.html
13. Zar JH: Biostatistical analysis. New Jersey, Prentice-Hall. 1999; 4th ed, pp. 663.
14. Taylor EN, Stampfer MJ, Curhan GC: Obesity, weight gain, and the risk of kidney stones. JAMA. 2005; 293: 455-62.
15. Alapont Pérez FM, Gálvez Calderón J, Varea Herrero J, Colome Borros G, Olaso Oltra A, Sánchez Bisono JR: Epidemiology of urinary lithiasis. Actas Urol Esp. 2001; 25: 341-9.
16. Martín JAL, García JRR, Castro SN, Gómez IR, Rosado EF, Castelo LA, et al.: Factores de riesgo metabólico em urolitiasis cálcica según el sexo y edad de los pacientes. Actas Urol Esp. 2006; 26: 111-20.
17. Siener R, Schade N, Nicolay C, von Unruh GE, Hesse A: The efficacy of dietary intervention on urinary risk factors for stone formation in recurrent calcium oxalate stone patients. J Urol. 2005; 173: 1601-5.
18. Moe OW, Preisig PA: Hypothesizing on the evolutionary origins of salt-induced hypercalciuria. Curr Opin Nephrol Hypertens. 2005; 14: 368-72.
19. Bonny O, Rubin A, Huang CL, Frawley WH, Pak CY, Moe OW: Mechanism of urinary calcium regulation by urinary magnesium and pH. J Am Soc Nephrol. 2008; 19: 1530-7.
20. Dirks JH: The kidney and magnesium regulation. Kidney Int. 1983; 23: 771-7.
21. Baxmann AC, Marques NC, Menon VB, Heilberg IP: Nutrição do paciente com nefrolitíase. In: Barros E, Gonçalves LF (ed.), Nefrologia no consultório. São Paulo, Artmed. 2007; pp. 475-83.
22. Borghi L, Schianchi T, Meschi T, Guerra A, Allegri F, Maggiore U, et al.: Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria. N Engl J Med. 2002; 346: 77-84.

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EDITORIAL COMMENT

The cause of urinary calculi is multifactorial as hereditary and environmental factors. The authors have showed no difference in food intake as calcium and animal protein of patients with idiopathic hypercalciuria (IH) and normocalciuria. Hypercalciuria is the evaluation for the calcium stone former, but in this study, authors did not study the composition of the stone. Several studies have reported that the common abnormal metabolic disorders are hypocitraturia and low urine volume, but in this study, urine citrate level is not low and different in both groups. Diet consumption is not the factor of IH in this study, patients need to be evaluated for the other factors such as absorptive, resorptive or renal hypercalciuria.

REFERENCE

1. Pak CY. Medical management of urinary stone disease. Nephron Clin Pract. 2004; 98: c49-53.

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Benign Prostatic Hyperplasia. Clinical Treatment Can Complicate Cataract Surgery

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ABSTRACT

Purpose: To investigate the effects of alpha-1 adrenergic receptor antagonists for the treatment of benign prostatic hyperplasia (BPH) regarding potential risks of complications in the setting of cataract surgery.
Aim: To address recommendations, optimal control therapy, voiding symptoms and safety within the setting of cataract surgery.
Materials and Methods: A comprehensive literature review was performed using MEDLINE with MeSH terms and keywords "benign prostatic hyperplasia", "intraoperative floppy iris syndrome", "adrenergic alpha-antagonist" and "cataract surgery". In addition, reference lists from identified publications were reviewed to identify reports and studies of interest from 2001 to 2009.
Results: The first report of intraoperative floppy iris syndrome (IFIS) was observed during cataract surgery in patients taking systemic alpha-1 AR antagonists in 2005. It has been most commonly seen related to use of tamsulosin. Changes of medication and washout periods of up to 2 weeks have been attempted to reduce the risk of complications in the setting of cataract surgery.
Conclusion: Patients under clinical treatment for BPH should be informed about potential risks of this drug class so that it can be discuss with their healthcare providers, in particular urologist and ophthalmologist, prior to cataract surgery.

Key words: *benign prostatic hyperplasia; alpha-blocker; floppy iris syndrome; cataract complication; tamsulosin*
Int Braz J Urol. 2010; 36: 563-70

INTRODUCTION

Benign prostatic hyperplasia (BPH) and cataract formation are common in older men. BPH affects nearly 3 out of 4 men by the age of 70 (1). Clinical management of BPH is often preferred to surgical treatment because surgery increases the risk of morbidities (2). Clinical treatments of symptomatic BPH include: 1) 5 alpha-reductase inhibitors, 2) alpha-1 adrenergic (alpha-1AAR) antagonists, and 3) a combination of a 5 alpha-reductase inhibitor and an alpha-1AAR antagonist. Currently, alpha-1AAR antagonists are an effective and commonly prescribed medication for BPH. These drugs improve urinary outflow by relaxing the smooth muscle in the prostate and bladder neck. There are four alpha-1AAR antagonists currently available in the United States: tamsulosin (selective alpha-1AAR antagonist subtype) and

three nonselective alpha-1AAR antagonist subtypes (alfuzosin, doxazosin, terazosin). The half-lives of the four available antagonists are similar, ranging from 10 to 22 hours (1,2). These drugs are used to treat lower urinary tract symptoms of BPH.

Cataracts are opacities within the natural crystalline lens of the eye that can result in impaired vision and even total blindness in advanced stages. Excision and replacement of the opacified lens with intraocular lens implants restores sight to 20/40 or greater in at least 90% of patients (3).

On the other hand, cataract surgery is the most commonly performed surgical procedure in the United States and in most developed countries. In 2001, over 1.6 million cataract surgeries were performed in the Medicare population alone. Reflecting the changing demographics of the U.S. population, the number of cataract extractions will increase substantially over the next quarter century (4).

Tamsulosin, an uroselective alpha-1AAR blocker, is believed to relieve the symptoms of BPH by relaxing the smooth muscle in the prostate and bladder neck through systemic blockade of alpha 1-adrenergic receptors. Because these receptors are present in the dilator smooth muscle of the iris, tamsulosin may also impede mydriasis during surgery and lead to intraoperative floppy iris syndrome (IFIS) (5). This complication was first described by Chang and Campbell in April 2005 (6), who identified IFIS in the intraoperative period in 63.0% (10/16) tamsulosin patients. In a prospective study of 900 consecutive cataract surgeries, the prevalence of IFIS was 2.2% (16/741 patients). Of these IFIS patients, ninety-four percent (15/16) were taking or had taken systemic tamsulosin (6).

MATERIALS AND METHODS

A comprehensive literature review was performed using MEDLINE with the MeSH terms and keywords "benign prostatic hyperplasia", "intraoperative floppy iris syndrome", "adrenergic alpha-antagonist" and "cataract surgery". In addition, reference lists from identified publications were reviewed to identify reports and studies of interest from 2001 to 2009.

BPH-IFIS AND ADRENERGIC RECEPTORS

BPH is the most common benign tumor in men with an incidence that is age-related. The etiology of BPH is not completely understood, but it seems to be multifactorial and endocrine controlled. BPH consists of two components: static (related to absolute size of the prostate gland) and dynamic (related to prostate smooth muscle contractions), that result clinically in lower urinary tract symptoms of BPH (urinary frequency, urgency, sensation of incomplete emptying, weak stream, straining to initiate urination). BPH is a common urological disorder in older men, and increases the risk of complications such as urinary retention, recurrent urinary tract infections, hematuria and bladder stones. The treatment goal for men with BPH links two different therapeutic classes: 1) 5-alpha reductase inhibitors (finasteride and dutasteride) and 2) alpha-1AAR antagonists. Tamsulosin is the most uroselective alpha-1AAR antagonist approved for use in the treatment of symptomatic BPH, which, although it improves urinary outflow, is also thought to inhibit the iris dilator smooth muscles causing varying degrees of IFIS (7-9). The effectiveness of tamsulosin is similar to other alpha-1AAR blocker drugs. Low dose preparations of tamsulosin provide similar benefits and have fewer side effects than higher dose preparations (9). Side effects of tamsulosin are generally mild but increase substantially at higher doses with common side effects including dizziness, rhinitis (runny nose and other cold-like symptoms) and abnormal ejaculation (9). The nonselective alpha-1AAR antagonists can cause orthostatic hypotension. Future studies should focus on complications in patients taking systemic alpha-1AAR antagonists before cataract surgery.

Adequate pupillary dilation and subsequent stability of the iris during surgery are important for successful and safe phacoemulsification (10). Chang and Campbell (6) described IFIS that occurred during cataract extraction surgery (phacoemulsification). They found that patients using systemic alpha-1AAR antagonists (tamsulosin) had an increase risk of iris complications during surgery. The initial description defined the following triad: floppy iris stroma that surges and billows in response to normal intraopera-

tive fluidics; prolapse of iris stroma due to surgical incisions despite well-constructed wounds; and progressive intraoperative miosis despite standard preoperative dilation. Recently, Chang et al. divided IFIS into a) mild IFIS: slight iris billowing, b) moderate IFIS: iris billowing and progressive miosis without prolapse and c) severe IFIS: presenting the triad of billowing, progressive miosis, and iris prolapse (11). With the aging of the population, an increasing number of elderly patients requiring cataract surgery chronically take alpha-1AAR antagonists. As currently available alpha-1AAR antagonist drugs are diffused to all tissues in the body, they would be expected to have effects such as relaxing the iris dilator smooth muscle. It is now clear that alpha-1AAR predominates and mediates contractions in the human prostate, urethra, and bladder neck.

IRIS, ALPHA ADRENORECEPTORS AND IFIS

The iris is, by far, a more complex tissue than originally recognized, with multiple layers and sources of innervation, as well as signaling systems that work together to regulate iris muscle tone (7). Functioning of the iris smooth muscle involves a complicated network of competing pathways (sympathetic, parasympathetic, serotonergic, dopaminergic and peptidergic), which also includes the prostaglandin and nitric oxide regulated pathways (7,12). Pupil size, both dilatation and constriction, is controlled by two muscles, the iris dilator and sphincter smooth muscles, each one with its own separate innervation and blood supply. Classically pupil dilation was thought to be mediated by a simple balance between sympathetic and parasympathetic nerve activity, via adrenergic receptors (AR) and muscarinic receptors, respectively. AR stimulation in the iris dilator smooth muscle causes contractions and consequently mydriasis.

In respect to the subtypes, iris contraction is 100-fold more sensitive to alpha-1AAR antagonists than to alpha-2 adrenergic antagonists, suggesting that alpha-1AAR antagonists predominate in sympathetically mediated iris dilator contraction; it has been observed that this subtype mediates iris dilator smooth muscle contractions in all species studied to date. Another structure where alpha-1AAR antagonists have potentially important effects is iris arterioles.

Friedman et al. (12) proposed that the blockade of receptors in blood vessel walls in patients taking tamsulosin is associated with vascular dysfunction of the vessels that supply the iris. These authors concluded that the iris vasculature provides the "skeletal" framework which supports the iris and that impairment of the smooth muscle of the iris arteriole wall damages this skeletal framework and leads to severe dysfunction. Both iris dilator contraction and vascular dysfunction actions can contribute to the IFIS observed in patients submitted to phacoemulsification who were taking this drug. Thus, patients taking tamsulosin may be at risk for IFIS during cataract surgery.

It has been suggested that long-term tamsulosin administration leads to a disuse atrophy of the muscular plate leading to poor pupil dilation and which could explain the flaccid nature of this tissue found during cataract surgery (13,14). This evidence needs further corroboration and additional scientific support.

Parssinën et al. (15) were the first authors to report finding tamsulosin in the aqueous humor after a pause in its use of up to 28 days, suggesting prolonged binding of tamsulosin to the iris and perhaps to the ciliary body. In our understanding, tamsulosin can cause long-term or possibly even permanent changes in iris function, the interval between the cessation of tamsulosin treatment and full recovery of the eye is uncertain and requires further investigation.

RECENT FINDINGS

BPH is one of the most common health problems in elderly men. Half of men older than 50 years and 90% of men older than 85 years have BPH (16). Cataracts also have a common occurrence in the elderly, with the incidence increasing with age and affecting 20% of individuals aged 65 to 74 years and 50% of those older than 75 years. BPH and cataracts go hand-in-hand in the elderly male population (17-19).

IFIS may occur within a few weeks of starting treatment using tamsulosin (11). This condition

is also seen, in smaller numbers, in patients treated with nonselective alpha-1AAR blockers (20). While the incidence of IFIS in the general population is reported to be between 0.6% and 2.2%, male patients prescribed tamsulosin develop the syndrome at a rate of 57% to 100% (6). Bell and colleagues (21) reported the results of a case-control analysis of a population-based retrospective cohort study using linked healthcare databases in Ontario, Canada. Among men aged 66 years or older who had cataract surgery between 2002 and 2007, 3,550 patients (3.7%) had had recent exposure to tamsulosin and 7.426 (7.7%) had had recent exposure to other alpha-1AAR blockers. Major ophthalmologic adverse events occurred in 284 patients (0.3%); these events were significantly more common among patients who had recently been taking tamsulosin (adjusted odds ratio: 2.33; 95% confidence interval: 1.22-4.43). These findings, regarding the serious consequences of tamsulosin-related IFIS in the 14-day period following cataract surgery, are most certainly the consequence of posterior capsular rupture, loss of lens fragments into the vitreous body, and vitreous loss. Retinal detachment is a potential consequence of these events and one of the most serious complications of IFIS. Thus, the result of the discontinuation of tamsulosin appears to be unpredictable and may not reliably reduce the severity of IFIS. Chang and Campbell (6) noted the occurrence of IFIS in patients who had stopped tamsulosin more than a year previously. The observations of Bell et al. (21) of a 14-day window in which complications occurred are directly related to the intraoperative difficulties produced by IFIS. To mitigate the potential intraoperative problems, several pharmacological and mechanical strategies have been proposed including preoperative dilation with strong cycloplegic agents such as atropine and homatropine or the intraoperative use of highly viscous agents, low flow of fluids into and out of the eye, iris retractors, and mechanical pupillary expansion rings (22). Following the report suggesting a strong link between tamsulosin and IFIS compared to other alpha-1 AR antagonists, case reports have been published of IFIS in men taking alfuzosin, doxazosin, and terazosin (23). Furthermore, saw palmetto (Serona repens), a widely used alternative therapy for BPH, is also reportedly associated with IFIS in 2 patients (24). Both patients had not taken prescription medications for BPH and developed moderate IFIS during cataract surgery. In contrast, a recent study has reported that nonselective alpha-1AAR antagonists are unlikely to be associated with IFIS (25).

However, many studies have advocated selectively discontinuing medications that increase risk for IFIS prior to cataract surgery. An alpha-1AAR antagonist washout period of up to 2 weeks prior to surgery has also been recommended (6). Again, the benefit of discontinuing these drugs prior to surgery has not been determined as IFIS has been reported several months after discontinuing therapy.

Furthermore, if cataract surgery is planned in the near future, patients and providers may elect to delay medical treatment for BPH until after surgery. The severity of symptoms and risk of BPH-related complications such as acute urinary retention should be considered against the potential complications related to cataract surgery. It is important that patients and providers make an educated decision on this matter. While there is still much to elucidate about the relationship between alpha-1AAR antagonists and IFIS, urologists should be knowledgeable when counseling patients about these emerging risks and their clinical significance and explain the importance of patients sharing their drug histories with their ophthalmologist prior to cataract surgery.

COMMENTS

Currently there is insufficient information to determine the exact underlying mechanism of IFIS. There are few reported studies large enough to assess the connection between tamsulosin exposure and postoperative complications. In addition, it is unclear whether proximity of therapy to the surgery is important or whether complications are equally likely with alpha-1AAR blockers other than tamsulosin (6). Studies have demonstrated more complications with tamsulosin than with other alpha-1AAR blocking drugs (6,21). This may relate to differences in receptor affinity with tamsulosin and with other related medications. It is believed that tamsulosin is more highly selective for alpha-1AAR antagonists than other alpha-1AAR blocker drugs (8). These particular

receptors are present in bladder-neck smooth muscle and in the iris dilator muscle. Blockage of the iris dilator smooth muscle allows unopposed action of the parasympathetically innervated iris constrictor muscle and loss of iris tone, resulting in clinical IFIS (8). Chang and Campbell (6) found that preoperatively discontinuing the medication for 4 to 7 days was helpful but not completely effective in preventing this syndrome. One patient manifested intra-operatively mild iris floppiness in both eyes but without the iris prolapse or pupil constriction necessary for the diagnosis of IFIS. On postoperative questioning, the patient described a history of tamsulosin use that was discontinued 3 years before the surgery. Some authors also report patients with true IFIS who had been off tamsulosin for 1 year, including patients reported in a prospective series. These observations may be consistent with the hypothesis of disuse atrophy of the dilator smooth muscle. Nevertheless, because it may increase the surgical pupil diameter, it is recommended that ophthalmologists, in consultation with urologists, consider temporarily discontinuing tamsulosin in patients for 1 to 2 weeks before surgery and using a maximum dilating regimen in the eyes of these patients (6).

In future studies it is important not only to enroll more patients, but also include clinical covariates in the analysis, age; coexisting diseases (e.g., diabetes, hypertension, congestive heart failure); concurrent drugs; intraoperative drugs administered (e.g., opioids or serotonergic drugs used for nausea/vomiting prophylaxis), and the doses of the alpha-1AAR antagonists taken by patients.

CONCLUSION

In the reviewed literature, we found a strong association between IFIS and the systemic use of the selective alpha-1AAR antagonist, tamsulosin, for BPH. However, new, randomized, placebo controlled, prospective studies are needed to determine the most effective management in patients with longstanding medical conditions requiring alpha-1AAR blockers and cataract surgery. Efforts will advance understanding, knowledge, and recognition of this syndrome which may lead to a lower incidence of surgical complications in patients with BPH undergoing cataract surgery.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Wei JT, Calhoun E, Jacobsen SJ: Urologic diseases in America project: benign prostatic hyperplasia. J Urol. 2008; 179(5 Suppl): S75-80.
2. McConnell JD, Roehrborn CG, Bautista OM, Andriole GL Jr, Dixon CM, Kusek JW, et al.: The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med. 2003; 349: 2387-98.
3. Powe NR, Schein OD, Gieser SC, Tielsch JM, Luthra R, Javitt J, et al.: Synthesis of the literature on visual acuity and complications following cataract extraction with intraocular lens implantation. Cataract Patient Outcome Research Team. Arch Ophthalmol. 1994; 112: 239-52. Erratum in: Arch Ophthalmol 1994; 112: 889.
4. Neff KD, Sandoval HP, Fernández de Castro LE, Nowacki AS, Vroman DT, Solomon KD: Factors associated with intraoperative floppy iris syndrome. Ophthalmology. 2009; 116: 658-63.
5. Blouin MC, Blouin J, Perreault S, Lapointe A, Dragomir A: Intraoperative floppy-iris syndrome associated with alpha1-adrenoreceptors: comparison of tamsulosin and alfuzosin. J Cataract Refract Surg. 2007; 33: 1227-34.
6. Chang DF, Campbell JR: Intraoperative floppy iris syndrome associated with tamsulosin. J Cataract Refract Surg. 2005; 31: 664-73.
7. Schwinn DA, Afshari NA: alpha(1)-Adrenergic receptor antagonists and the iris: new mechanistic insights into floppy iris syndrome. Surv Ophthalmol. 2006; 51: 501-12.

8. Cantrell MA, Bream-Rouwenhorst HR, Steffensmeier A, Hemerson P, Rogers M, Stamper B: Intraoperative floppy iris syndrome associated with alpha1-adrenergic receptor antagonists. Ann Pharmacother. 2008; 42: 558-63.
9. Lee M: Alfuzosin hydrochloride for the treatment of benign prostatic hyperplasia. Am J Health Syst Pharm. 2003; 60: 1426-39. Erratum in: Am J Health Syst Pharm. 2004; 61: 437.
10. Cheung CM, Awan MA, Sandramouli S: Prevalence and clinical findings of tamsulosin-associated intraoperative floppy-iris syndrome. J Cataract Refract Surg. 2006; 32: 1336-9.
11. Chang DF, Osher RH, Wang L, Koch DD: Prospective multicenter evaluation of cataract surgery in patients taking tamsulosin (Flomax). Ophthalmology. 2007; 114: 957-64.
12. Friedman AH: Tamsulosin and the intraoperative floppy iris syndrome. JAMA. 2009; 301: 2044-5.
13. Bidaguren A, Irigoyen C, Mendicute J, Gutiérrez E, Gibelalde A, Ubeda M: Floppy-iris syndrome associated with tamsulosin. A prospective case-control study. Arch Soc Esp Oftalmol. 2007; 82: 349-54.
14. Leibovici D, Bar-Kana Y, Zadok D, Lindner A: Association between tamsulosin and intraoperative "floppy-iris" syndrome. Isr Med Assoc J. 2009; 11: 45-9.
15. Pärssinen O, Leppänen E, Keski-Rahkonen P, Mauriala T, Dugué B, Lehtonen M: Influence of tamsulosin on the iris and its implications for cataract surgery. Invest Ophthalmol Vis Sci. 2006; 47: 3766-71.
16. Roehrborn CG, Schwinn DA: Alpha1-adrenergic receptors and their inhibitors in lower urinary tract symptoms and benign prostatic hyperplasia. J Urol. 2004; 171: 1029-35.
17. Tiwari A: Tamsulosin and floppy iris syndrome in benign prostatic hyperplasia patients. Expert Opin Investig Drugs. 2006; 15: 443-6.
18. Abdel-Aziz S, Mamalis N: Intraoperative floppy iris syndrome. Curr Opin Ophthalmol. 2009; 20: 37-41.
19. Leonardi A, Hieble JP, Guarneri L, Naselsky DP, Poggesi E, Sironi G, et al.: Pharmacological characterization of the uroselective alpha-1 antagonist Rec 15/2739 (SB 216469): role of the alpha-1L adrenoceptor in tissue selectivity, part I. J Pharmacol Exp Ther. 1997; 281: 1272-83.
20. Mamalis N: Intraoperative floppy-iris syndrome associated with systemic alpha blockers. J Cataract Refract Surg. 2008; 34: 1051-2.
21. Bell CM, Hatch WV, Fischer HD, Cernat G, Paterson JM, Gruneir A, et al.: Association between tamsulosin and serious ophthalmic adverse events in older men following cataract surgery. JAMA. 2009; 301: 1991-6.
22. Gurbaxani A, Packard R: Intracameral phenylephrine to prevent floppy iris syndrome during cataract surgery in patients on tamsulosin. Eye (Lond). 2007; 21: 331-2.
23. Venkatesh R, Veena K, Gupta S, Ravindran RD: Intraoperative floppy iris syndrome associated with terazosin. Indian J Ophthalmol. 2007; 55: 395-6.
24. Yeu E, Grostern R: Saw palmetto and intraoperative floppy-iris syndrome. J Cataract Refract Surg. 2007; 33: 927-8.
25. Chadha V, Borooah S, Tey A, Styles C, Singh J: Floppy iris behaviour during cataract surgery: associations and variations. Br J Ophthalmol. 2007; 91: 40-2.

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EDITORIAL COMMENT

This detailed review/up-to-date paper is a great opportunity to call the attention of physicians and patients about the intraoperative floppy iris syndrome (IFIS), since several ophthalmologists, as well as urologists and general physicians, still are not familiarized with it.

IFIS is a recently described (2005) drug related condition, associated to higher morbidity in cataract surgery in patients on systemic sympathetic alpha-1 antagonist medications for benign prostatic hypertrophy (BPH). This syndrome is characterized by a triad of intraoperative features during phacoemulsification: 1) a flaccid iris that undulates and billows in response to ordinary intraocular surgical fluid currents; 2) a propensity for the floppy iris to prolapse towards surgical incisions and aspiration port of the phacoemusification machine handpiece; and 3) progressive intraoperative pupil constriction.

Good pupil dilation throughout the surgery is important to facilitate the extraction of the opacified lens. Miosis (pupillary constriction) and iris laxity not only make the surgery longer and more stressful, but are associated to complications that can compromise permanently the vision of the operated eye, like iris damage, more inflammation, vitreous loss and retinal detachment.

There are some ways to manage this miotic and floppy iris. The use of atropine, intraoperative phenylephrine and pupil expansion devices are some examples of strategies that decrease surgical complications. The biggest problem is when the cataract surgeon is not aware of the possibility of IFIS in their patient.

Systemic alpha-1 adrenergic antagonists are commonly used for BPH, since they improve bladder emptying and reduce urinary frequency by relaxing the smooth muscle in the prostate and bladder neck. These drugs are also prescribed for hypertension, urinary retention and as an adjunct for the treatment of renal calculi, which make women susceptible to IFIS too. Studies have shown that IFIS is more frequent and severe in patients using selective alpha-1 antagonists drugs (to alpha-1A subtype receptors, more common at the prostate and probably in the iris too), like tamsulosin (Flomax) and maybe silodosin. IFIS has also been associated with saw palmetto (Serenoa repens) and a variety of other medications, including antipsychotic drugs that may possess some alpha-antagonistic effects.

Although it would seem logical, the utility of stopping tamsulosin preoperatively remains controversial and of unproven benefit. Also, there is a risk for causing acute urinary retention, but it is believed to be small. The serum half-life of tamsulosin is approximately 48 to 72 hours, associated to a prolonged drug-receptor binding time. In addition, there are some evidences that IFIS can occur shortly after the drug is initiated.

As well described in this paper, the IFIS pathophysiology seems to involve iris vascular dysfunction secondary to the alpha-1 antagonists. This would damage the iris skeletal framework. In addition, the iris dilator muscle action decreases, showing some atrophy. Both factors would lead to severe and permanent iris malfunction.

The prevalence of BPH, as well as cataract, increases with age and tend to be more frequent as the population ages. Studies have shown the prevalence of men receiving tamsulosin for BPH among the patients operated for cataract around 1-3%. Moreover, 52-90% of the patients receiving tamsulosin presented at least one manifestation of IFIS.

Medical societies and public agencies have taken several measures in order to better divulgate IFIS. The American Society of Cataract and Refractive Surgery (ASCRS) first issued a global advisory alert regarding tamsulosin in January 2005. The US Food and Drug Administration instituted a labeling warning about alpha-1 antagonists and cataract surgery in the same year. The ASCRS, American Academy of Ophthalmology (AAO), and American Urological Association issued a joint press release in 2006 highlighting the need for patients taking systemic alpha-1 antagonists to inform their ophthalmologist before cataract surgery. Soon after, this message was incorporated into the direct-to-consumer advertisements for Flomax. ASCRS and the AAO also issued a joint educational update statement in July 2008 that was disseminated by the American College of Physicians and the American Academy of Family Physicians to

more than 200000 members. For patients with known cataracts, prescribing physicians were asked to consider involving the cataract surgeon before initiating chronic tamsulosin or alpha-1 antagonist treatment.

More research should be done to better clarify this drug related syndrome and prevent patients under treatment for BPH to have eyesight complications in cataract surgery.

REFERENCES

1. Chang DF, Campbell JR: Intraoperative floppy iris syndrome associated with tamsulosin (Flomax). J Cataract Refract Surg. 2005; 31:664-673.
2. Chang DF, Osher RH, Wang L, Koch DD: Prospective multicenter evaluation of cataract surgery in patients taking tamsulosin (Flomax). Ophthalmology. 2007; 114: 957-64.
3. Chang DF, Braga-Mele R, Mamalis N, Masket S, Miller KM, Nichamin LD, et al.: ASCRS White Paper: clinical review of intraoperative floppy-iris syndrome. J Cataract Refract Surg. 2008; 34: 2153-62.

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EDITORIAL COMMENT

The authors showed in this interesting review the unexpected relationship between two entities: benign prostatic hyperplasia (BPH) and cataract. The use of tamsulosin, a selective alpha1- adrenergic antagonist used in the treatment of BPH, may lead to the development of intra-operative floppy iris syndrome (IFIS) and interfere with the dilation of the pupil. Interestingly, cases of IFIS during cataract surgery have been reported in patients under treatment for BPH with other drugs such as finasteride, also used for BPH treatment (1).

The technique of phacoemulsification for cataract extraction has gained popularity in the last decade. In this modern surgery, the lens is broken by ultrasound and extracted from the eye through a combination of irrigation and aspiration of fluids. The instability of the iris and inadequate pupillary dilation during surgery can make this dynamic surgery, technically, more difficult. Facio et al. have shown the importance of careful selection of patients and planning for both BPH treatment and cataract surgery, emphasizing the necessity of a multidisciplinary approach by urologists and ophthalmologists in such cases.

REFERENCE

1. Issa SA, Dagres E: Intraoperative floppy-iris syndrome and finasteride intake. J Cataract Refract Surg. 2007; 33: 2142-3.

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Are There Differences in Zonal Distribution and Tumor Volume of Prostate Cancer in Patients with a Positive Family History?

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ABSTRACT

Purpose: To determine if there are any differences in the zonal distribution and tumor volumes of familial and sporadic prostate cancers (PC) in men undergoing radical prostatectomy.
Material and Methods: 839 patients underwent a radical prostatectomy in the absence of prior neoadjuvant therapy between 1987 and 1996. Telephone interviews were conducted to obtain an updated family history. A positive family history was defined as the diagnosis of PC in at least one first degree relative. Prostatectomy specimens were examined to determine the number of tumor foci, zonal origin of the dominant tumor focus, tumor volume of the largest cancer focus, total tumor volume, Gleason score and stage, and the surgical margin status. Results were stratified according to family history and ethnicity.
Results: We successfully contacted 437 patients (52%). Prostatectomy specimens from 55 patients were excluded from review due to a history of prior transurethral resection of the prostate
(n = 26) or uncertain pathological stage (n = 29). Of the remaining 382 patients, 76 (20%) reported having a first-degree relative with PC. Statistical analysis revealed no significant differences in the pathologic variables between the two groups of patients with or without a family history of PC.
Conclusions: Familial and sporadic PC share similar characteristics. No histopathological differences account for the increased positive predictive value of PC screening tests among patients with a family history of PC.

Key words: *prostatic neoplasms; tumor burden; family characteristics; tumor volume; pathology*
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INTRODUCTION

The reported rate of positive family history among men with prostate cancer (PC) ranges from 13% to 26% and approaches 40% for men diagnosed with the disease before age 55 (1-3). Detection of cancer in multiple first-degree or second-degree relatives coupled with early age at cancer diagnosis substantially increases a man's relative risk and absolute risk of developing PC (4).

Whereas a number of earlier studies evaluated family history and radical prostatectomy (RP) pathology to determine the significance of a positive family history as a risk factor for PC, they were directed largely at the number of tumors, the pathologic stage, and outcome measures including biochemical disease-

free survival (DFS) and overall survival (5-9). Very little information is available on the zonal distribution of cancers in patients with a positive family history. Furthermore, there are no pathologic data that explain the increased positive-predictive value reported for abnormal digital rectal examination (DRE) and prostate-specific antigen (PSA) tests in high-risk patients, such as those with a positive family history (10,11). We as well do not currently know if there exist differences in terms of tumor volumes between patients with and without a family history of PC?

We hypothesized that RP specimens from patients with a family history of PC might reveal different tumor characteristics compared with specimens from patients with sporadic PC and that the different characteristics could account for the higher diagnostic yield of prostate biopsies performed in patients with risk factors for disease. To address this hypothesis, we specifically examined the zonal distribution of cancer foci, tumor location, and tumor volume differences of our surgically managed patients with and without a family history of PC. We also analyzed corresponding clinicopathologic data, such as age, preoperative PSA levels, pathologic stage, Gleason score, and surgical margin status in patient groups stratified by family history.

MATERIALS AND METHODS

A research protocol was designed and approved by our Institutional Review Board prior to the initiation of this study. From January 1987 to December 1996, 839 patients underwent RP at The University of Texas M. D. Anderson Cancer Center, with no prior neoadjuvant therapy. The patients were followed for at least 6 years from the time of RP. Family history data were obtained by telephone interview to update the patient's file and to capture additional family members affected with PC since the index patient's surgical procedure. The patients and immediate family members who were successfully contacted were included in the study. Positive family history was defined as having at least 1 first-degree relative (e.g., brother, son, father) who had a diagnosis of PC. Only a few patients with possible hereditary prostate cancer (HPC) were included in the analysis. HPC is believed to be transmitted in an autosomal dominant fashion, and it is postulated that HPC accounts for 5% to 10% of all cases of PC (and possibly 30% to 45% of early onset cancers). To be classified as having HPC, patients had to fulfill one of the following clinical criteria: PC occurring in 3 successive generations (maternal or paternal side), 3 cases of PC diagnosed within a nuclear family, or 2 men within a single family diagnosed with PC before age 55 (4,12).

The prostatectomy specimens were evaluated as previously reported (13,14). Each tumor focus was outlined on the histologic sections, and the total number of tumor foci as well as the zonal origin of each tumor focus were recorded. Zones were categorized as peripheral zone (PZ), transition zone (TZ), or multiple zones (MZ). An area of carcinoma was considered a different focus if it was separated by a low-power field diameter (4.5 mm) from the nearest adjacent focus, as reported previously (15). Tumor location was recorded according to standardized guidelines (Figure-1). Each tumor focus was graded according to the Gleason grading system (16). The Gleason score assigned to the specimen was that of the tumor focus with the highest Gleason score. The volume of each tumor focus was calculated according to the three-dimensional volume estimation method (17). The 2002 American Joint Committee on Cancer tumor-node-metastasis staging system was used to define organ-confined cancers (T2), established extraprostatic extension (T3a), and cancer involvement of the seminal vesicles (T3b). Patients with positive margins without extraprostatic extension were categorized as having T2 tumors regardless of margin status.

Patients' demographic and clinical characteristics were summarized by family history status. Fisher's exact test was performed to assess the association between categorical variables. The Wilcoxon rank sum test was performed to assess the difference in continuous variables between patients with and those without a family history of PC. In order to assess the predictive effect of family history and ethnicity simultaneously, a multinomial logistic regression model was fit for the outcome variable of "site of dominant tumor focus", which can take the values of "PZ", "TZ", or "MZ". The fitted multinomial logistic regression model can be written as follows:

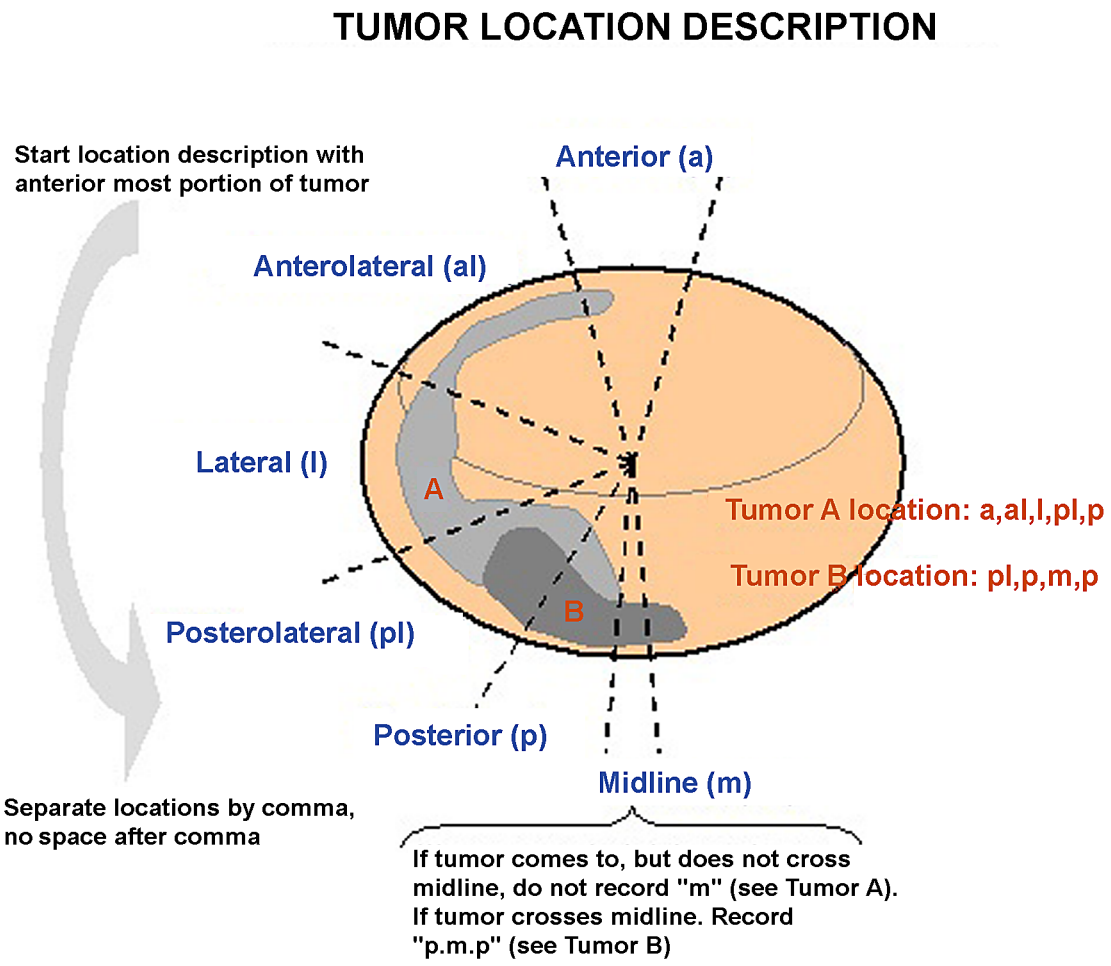

Figure 1 *– Guidelines to record tumor location description.*

$$pr(\gamma_i = 1|x_i) = \frac{1}{1 + \Sigma^{j}_{j=2} \exp(x_i\beta_j)} \text{ for } m = 1$$

$$pr(\gamma_i = m|x_i) = \frac{\exp(x_i\beta_m)}{1 + \Sigma^{j}_{j=2} \exp(x_i\beta_j)} \text{ for } m > 1$$

where y_i is the response variable for subject i, and can take values of 1, 2, …, m. In our case, the site of dominant tumor focus could be "P", "T" or "M"; therefore, m = 3. X_i is vector of covariates for subject i (here, are family history and ethnicity) and β_j is the vector of coefficient, with j ranges from 2 to J. Note: J = m. All statistical analyses were carried out in SAS or Splus software program.

RESULTS

Patient Characteristics

We successfully contacted 437 (52%) patients. Specimens from 55 patients were excluded from review due to the patient's history of prior

Table 1 – *Demographic and clinical characteristics.*

Variable	Negative FHx (N = 306)	Positive FHx (N = 76)	p Value
Age	63.2 (42.3 - 74.7)	62.8 (46.7 - 72.2)	0.43
% >= 60 years	207 (67.6%)	49 (64.5%)	0.70
Total Tumor volume	1.64 (0.02 - 17.44)	1.72 (0.04 - 9.56)	0.27
Tumor volume of largest cancer focus	1.20 (0.02 - 14.40)	1.36 (0.04 - 7.68)	0.44
Prostate Weight (g)	40 (10 - 141)	40 (18 - 95)	0.90
Total tumor volume/ Prostate Weight	0.038 (0.00046 - 0.31)	0.044 (0.0005 - 0.25)	0.27
Ethnicity			0.61
Caucasian	266 (86.9%)	70 (92.1%)	
African American	23 (7.5%)	4 (5.3%)	
Hispanic	15 (4.9%)	2 (2.6%)	
Other	2 (0.7%)	0 (0.0%)	
Diagnostic PSA	7.5 (0.7 - 55.0)	7.6 (1.3 - 30.1)	0.50
Pathologic Gleason Score			0.13
5,6	31 (10.1%)	14 (18.4%)	
7	190 (62.1%)	42 (55.3%)	
8,9	85 (27.8%)	20 (26.3%)	
Pathologic Stage			0.44
T2	209 (68.3%)	46 (60.5%)	
T3a	74 (24.2%)	23 (30.3%)	
T3b	23 (7.5%)	7 (9.2%)	
Surgical Margins			0.52
Negative	231 (75.5%)	54 (71.1%)	
Positive	75 (24.5%)	22 (28.9%)	

T2 = organ confined; T3a = established extracapsular tumor; T3b = seminal vesicle involvement by tumor; FHx = family history.

transurethral prostatectomy (n = 26), uncertain or missing pathologic data (n = 29), leaving 382 patients with complete clinical and pathologic data. Seventeen patients (4%) were believed to have HPC on the basis

Table 2 *– Characterization of affected family members in familial prostate caner cases (includes possible hereditary cancers).*

Affected Relatives in Index Patients with 1st Degree Family History (N = 76)	
One Relative (N = 59)	Number of Affected Relatives
Father	33
Brother	25
Son	1
Two Relatives (N = 15)	
Father, Brother	5
Father, Grandfather	5
Brother, Brother	4
Brother, Grandfather	1
Four Relatives (N = 2)	
Brothers (x4)	2
Categories of Possible Hereditary Prostate Cancer (n = 17)	
	Number of Cases
At least three men within same nuclear family	11
Three successive generations	5
Age < 55 in index patient and at least 1 relative	1

of the aforementioned clinical criteria. Table-1 lists clinical information and demographics of the patients with and without a family history of PC. There was no difference in any of the clinical or pathologic features including total tumor volume and tumor volume of the largest tumor focus among patients with and without a family history of PC. Table-2 characterizes the affected family members in familial prostate cancer and hereditary prostate cancer cases.

Association between Family History, Ethnicity, and Pathologic Features

The association between family history of PC and pathologic stage was evaluated in Caucasian and other ethnicities (Table-3). No significant association was detected in either Caucasian ($p = 0.46$) or African American patients ($p = 0.18$). To further clarify the potential association between location of the largest cancer foci and ethnicity, we assessed the location of cancer foci by familial history of prostate cancer (Table-4). We were unable to show an association between the location of the largest cancer focus and familial history of prostate cancer, with substratification of the volume of the largest cancer focus (< 0.5 cc, 0.5 to 1.5 cc, and > 1.5 cc). Similarly, we attempted to determine if there was an association between the location of the second largest cancer focus and family history of prostate cancer (Table-4), with no statistically signification association noted. Table-5 shows the location of the dominant tumor focus according to the patient's reported family history and race. Positive family history of PC did not significantly impact ($p = 0.73$) the dominant tumor focus. On multinomial logistic regression analysis, the lack of association between ethnicity and site of dominant tumor focus was preserved (Tables 6 and 7). Furthermore, we compared the number of tumor foci based on either family history or ethnicity (Table-8). The mean and median number of tumor foci did not show a significant difference based on family history of PC or ethnicity.

Table 3 – *Pathologic T stage stratified by family history and ethnicity.*

Ethnicity	Pathologic T-stage	Negative Family History	Positive Family History	p Value
Caucasian				0.46
	T2	180 (67.7%)	42 (60.0%)	
	T3a	65 (24.4%)	22 (31.4%)	
	T3b	21 (7.9%)	6 (8.6%)	
African American				0.18
	T2	16 (69.6%)	3 (75.0%)	
	T3a	6 (26.1%)	0 (0.0%)	
	T3b	1 (4.3%)	1 (25.0%)	

T2 = organ confined; T3a = established extracapsular tumor; T3b = seminal vesicle involvement by tumor.

COMMENTS

Most physicians recommend early screening for PC in populations at high risk for the disease. High-risk populations include men with a positive family history of PC and African American men (18). The risk is even greater for men with multiple risk factors or for those whose affected relatives were diagnosed with cancer at younger ages (less than 55-60 years of age) (4).

Several studies have sought the patterns of RP pathology that could be unique to patients with a family history of PC. Studies have focused on the number of tumors, Gleason score, pathologic stage, and biochemical DFS and cancer-specific survival rates (1,5-9). However, there is very little information about the zonal distribution of prostate cancer in patients with a positive family history. Similarly, tumor volume has been shown to be an independent predictor of biochemical failure yet there is little to no information on the association between either tumor volume (either total or of the dominant focus of prostate cancer) among patients with or without a family history of PC (13,19).

Prostate cancer is characterized as a multifocal disease, and the majority of cancers are located in the PZ area most commonly targeted and sampled during prostate biopsies. Catalona et al. (10) reported that there is a higher positive predictive value of PC screening tests (PSA and DRE) for detecting PC in patients with established risk factors such as family history and African American ethnicity while controlling for both age and PSA. It seems intuitive that prostatectomy specimens from patients with risk factors for disease might contain more dominant tumor foci located peripherally in targeted biopsy zones, a greater number of tumor foci, or a greater percentage of cancer per prostate specimen to account for the significantly higher yield of prostate biopsies. However, our pathology results do not support the hypothesis that differences in the zonal origin of the dominant tumor focus or differences in the number of tumor foci could account for higher cancer detection rates in patients with PC risk factors. There were no significant differences in the mean number of tumor foci based on family history or on ethnicity. Most dominant tumor foci were located peripherally and family history did not alter the distribution of the dominant tumor foci between the PZ, TZ, or MZ. Contrary to family history status, when the locations of the dominant tumor foci were stratified according to ethnicity, non-Caucasians were demonstrated to have more dominant tumor foci originating within the transition zone compared to Caucasian patients.

In an attempt to clarify if the location of the largest and second largest tumor foci were different based on family history of PC, we were unable to identify an association between site of these predominant tumor foci and familial history of PC. This may have had important clinical implications in terms of the

Table 4 *– The association between location of tumor foci and family history within patients having largest tumor and second largest tumor less than 0.5 cc, between 0.5 cc and 1.5 cc, and greater than 1.5 cc.*

Location	**Family History**		
	Negative	**Positive**	
Largest Tumor			**p Value**
< 0.5 cc.			
L,PL,P	10 (16.7)	1 (8.3)	0.78
PL	23 (38.3)	5 (41.7)	
PL,P	16 (26.7)	5 (41.7)	
L,PL	10 (16.7)	1 (8.3)	
L	1 (1.7)	0 (0)	
0.5 - 1.5 cc.			
L,PL,P	42 (52.5)	15 (50)	0.71
PL	4 (5)	2 (6.7)	
PL,P	13 (16.2)	4 (13.3)	
L,PL	13 (16.2)	4 (13.3)	
AL,L,PL,P	8 (10)	4 (13.3)	
L	0 (0)	1 (3.3)	
> 1.5 cc.			
L,PL,P	21 (48.8)	4 (50)	1.00
PL,P	4 (9.3)	1 (12,5)	
L,PL	1 (2.3)	0 (0)	
AL,L,PL,P	17 (39.5)	3 (37.5)	
Second largest tumor			
< 0.5 cc.			
L,PL,P	56 (38.6)	17 (41.5)	0.45
PL	21 (14.5)	7 (17.1)	
PL,P	27 (18.6)	8 (19.5)	
L,PL	21 (14.5)	4 (9.8)	
AL,L,PL,P	20 (13.8)	4 (9.8)	
L	0 (0)	1 (2.4)	
0.5 - 1.5 cc.			
L,PL,P	21 (48.8)	4 (50)	0.4
PL,P	4 (9.3)	1 (12,5)	
L,PL	1 (2.3)	0 (0)	
AL,L,PL,P	17 (39.5)	3 (37.5)	
> 1.5 cc.			
L,PL,P	2	0	0.4

A = Anterior; AL: anterolateral; L = lateral; P: posterior; PL = posterolateral. P values determined using Fisher's exact test.

Table 5 – *Site of dominant tumor focus stratified by family history and ethnicity.*

	Dominant Tumor Focus			
	PZ	**TZ**	**MZ**	**p Value**
Family History				0.73
Negative	242 (79.1%)	59 (19.3%)	5 (1.6%)	
Positive	64 (84.2%)	11 (14.5%)	1 (1.3%)	
Ethnicity				0.06
Caucasian	275 (81.8%)	56 (16.7%)	5 (1.5%)	
All Others	31 (67.4%)	14 (30.4%)	1 (2.2%)	
African American	17 (63.0%)	9 (33.3%)	1 (3.7%)	0.04
All Others	289 (81.4%)	61 (17.2%)	5 (1.4%)	

PZ = peripheral zone; TZ =transition zone; MZ = multiple zones.

transrectal ultrasound guided prostatic biopsy schemes to apply to patients based on familial history of PC. However, due to the lack of an association between the site of the largest and second largest tumor focus and family history of PC, an extensive biopsy scheme consisting of 10 to 12 biopsy cores should be obtained in all patients in whom prostatic biopsies are clinically indicated.

Racial variation in the location of dominant tumor foci has been reported previously. Pettaway and colleagues found that 35% of all tumor foci in African American men were of TZ origin compared with 21% of the tumor foci in a group of Caucasian patients matched according to pathologic stage. In this same study, the median number of tumor foci and the overall prostatic tumor volumes (stratified by pathologic stage and zone of origin of the cancers) were not statistically different (20). Pettaway et al. hypothesized that the TZ epithelium in African American patients might be more susceptible to malignant transformation compared with the TZ epithelium of Caucasian men (20).

A smaller study failed to reveal significant differences in tumor multifocality and the zonal distribution of tumor foci in patients with a positive family history. Bastacky et al. (21) examined the morphologic characteristics of 81 radical prostatectomy specimens from selected small groups of patients with sporadic PC, familial PC, and HPC. In this study, patients with sporadic PC had a mean 7.3 tumor foci per

Table 6 – *Fitted multinomial logistic regression model for zone distribution.*

Parameter	**Zone**	**Estimate**	**Standard Error**	**Probability > Chi Sq**	**Point Estimate**	**95% CI**
Intercept	TZ	-1.4944	0.1536	< 0.0001		
Intercept	MZ	-4.0096	0.4906	< 0.0001		
FH (pos vs. neg)	TZ	-0.3282	0.3590	0.36	0.72	0.356-1456
FH (pos. vs. neg)	MZ	-0.2464	1.1066	0.82	0.78	0.089-6.838
Black vs. Others	TZ	0.9050	0.4364	0.04	2.47	1.051-5.815
Black vs. Others	MZ	1.2126	1.1246	0.28	3.36	0.371-30.468

FH = family history; MZ = multiple zones; TZ = transition zone.

Table 7 – *Fitted multinomial logistic regression model for zone distribution.*

Parameter	Zone	Estimate	Standard Error	Probability > Chi Sq	Point Estimate	95% CI
Intercept	TZ	-1.5327	0.1598	< .0001		
Intercept	MZ	-3.9581	0.4924	< .0001		
FH (pos vs. neg)	TZ	-0.3054	0.3595	0.40	0.737	0.364-1.491
FH (pos. vs. neg)	MZ	-0.2503	1.1069	0.82	0.779	0.089-6.815
Non-White vs. White	TZ	0.7756	0.3548	0.03	2.172	1.083-4.354
Non-White vs. White	MZ	0.5559	1.1140	0.62	1.743	0.196-15.477

FH = family history; MZ = multiple zones; TZ = transition zone.

gland compared with a mean 5.2 tumor foci per gland in the familial PC group. On the contrary, patients with familial PC had a larger volume of cancer per gland compared with the sporadic PC group (3.3 cm^3 vs. 2.4 cm^3). However, these results failed to reach statistical significance likely due to the small number of patients in each of the three groups.

Although patients with a positive family history of PC are at higher risk of developing the disease, most studies suggest that these patients have either equivalent (12) or more favorable disease characteristics, such as lower Gleason scores (1,7,21) or less extracapsular tumor extension (9). Furthermore, there is no convincing evidence that survival is better or worse for patients with a positive family history of PC undergoing RP (5,8,9) or primary radiation therapy (22) compared to patients with sporadic PC. Surprisingly, only one group reported differences in biochemical DFS following RP or primary radiation therapy favoring patients with sporadic PC. Even in this study, there were no clinical or pathologic differences to account for the inferior biochemical outcome for patients with a positive family history (6). Regardless of the disease outcome, no study to date (including our report) has been able to demonstrate different pathologic or morphologic characteristics in prostate specimens from patients with a positive family history compared with patients without a family history of PC that would account for an approximately 10% increase in the positive predictive value of current diagnostic screening tests (PSA and DRE) on PC detection (10,11,23). Consistent with previous reports, our study revealed no significant differences between patients with a family history of

Table 8 – *Mean number of tumor foci stratified by family history and ethnicity.*

	Number of Tumor Foci		
	Mean	**Median** (range)	**p Value**
Family History			
Negative	3.31	3 (1 - 10)	0.55
Positive	3.18	3 (1 - 8)	
Ethnicity			
Caucasian	3.27	3 (1 - 10)	0.32
All others	3.41	3 (1 - 7)	
African American	3.52	3 (1 - 7)	0.29
All others	3.27	3 (1 - 10)	

PC compared to patients without a family history of PC in terms of age, preoperative PSA, Gleason score, pathologic stage, and surgical margin status. We did not examine disease-specific or biochemical DFS. Based on the pathologic results from both patient groups, it is unlikely that there would be meaningful differences in these outcome measures.

Several potential biases with this study deserve mention. Although our data were stratified according to ethnicity, few non-Caucasian patients were included in the overall analysis. Patients included in this study all underwent RP. Thus, our population may not represent the full spectrum of familial and sporadic PC. Other potential risk factors, such as obesity and diet, may significantly affect cancer initiation, promotion, and progression, and were not accounted for in this analysis (24,25). Regarding family history, we did not confirm reported positive family histories with pathology reports of affected relatives. Neither were we able to accurately determine the exact age of most of the affected family members at the time of their own diagnosis. However, recognizing some of these potential biases at study onset, we did not rely on medical record family history data for study inclusion, thus excluding nearly half of the patients undergoing RP during the study period. We attempted to clarify and update family history data via telephone interviews with the patients or with their immediate family members. However, an accurate assessment of the significance of family history related to the development of PC will be limited as long as the definition of a positive family history is based on clinical criteria and not on molecular fingerprints or biomarkers that might establish a true familial link to PC among affected individuals.

CONCLUSIONS

Patients with familial and sporadic PC have pathologically and morphologically similar tumors. In our study group, there were no clinically significant differences in the zonal origin and location of the dominant tumor foci, tumor volume, or number of tumor foci to account for the reported increased positive predictive value of diagnostic screening tests in patients with a family history of PC.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Keetch DW, Humphrey PA, Smith DS, Stahl D, Catalona WJ: Clinical and pathological features of hereditary prostate cancer. J Urol. 1996; 155: 1841-3.
2. Bratt O, Kristoffersson U, Lundgren R, Olsson H: Familial and hereditary prostate cancer in southern Sweden. A population-based case-control study. Eur J Cancer. 1999; 35: 272-7.
3. Carter BS, Beaty TH, Steinberg GD, Childs B, Walsh PC: Mendelian inheritance of familial prostate cancer. Proc Natl Acad Sci U S A. 1992; 89: 3367-71.
4. Bratt O: Hereditary prostate cancer: clinical aspects. J Urol. 2002; 168: 906-13.
5. Azzouzi AR, Valeri A, Cormier L, Fournier G, Mangin P, Cussenot O: Familial prostate cancer cases before and after radical prostatectomy do not show any aggressiveness compared with sporadic cases. Urology. 2003; 61: 1193-7.
6. Kupelian PA, Kupelian VA, Witte JS, Macklis R, Klein EA: Family history of prostate cancer in patients with localized prostate cancer: an independent predictor of treatment outcome. J Clin Oncol. 1997; 15: 1478-80.
7. Kotsis SV, Spencer SL, Peyser PA, Montie JE, Cooney KA: Early onset prostate cancer: predictors of clinical grade. J Urol. 2002; 167: 1659-63.
8. Grönberg H, Damber L, Tavelin B, Damber JE: No difference in survival between sporadic, familial and hereditary prostate cancer. Br J Urol. 1998; 82: 564-7.
9. Norrish AE, McRae CU, Cohen RJ, Jackson RT: A population-based study of clinical and pathological prognostic characteristics of men with familial and sporadic prostate cancer. BJU Int. 1999; 84: 311-5.

10. Catalona WJ, Antenor JA, Roehl KA, Moul JW. Screening for prostate cancer in high risk populations. J Urol. 2002; 168: 1980-3; discussion 1983-4.
11. Aprikian AG, Bazinet M, Plante M, Meshref A, Trudel C, Aronson S, et al.: Family history and the risk of prostatic carcinoma in a high risk group of urological patients. J Urol. 1995; 154: 404-6.
12. Carter BS, Bova GS, Beaty TH, Steinberg GD, Childs B, Isaacs WB, et al.: Hereditary prostate cancer: epidemiologic and clinical features. J Urol. 1993; 150: 797-802.
13. Babaian RJ, Troncoso P, Steelhammer LC, Lloreta-Trull J, Ramirez EI: Tumor volume and prostate specific antigen: implications for early detection and defining a window of curability. J Urol. 1995; 154: 1808-12.
14. Sanchez-Ortiz RF, Troncoso P, Babaian RJ, Lloreta J, Johnston DA, Pettaway CA: African-American men with nonpalpable prostate cancer exhibit greater tumor volume than matched white men. Cancer. 2006; 107: 75-82.
15. Troncoso P, Babaian RJ, Ro JY, Grignon DJ, von Eschenbach AC, Ayala AG: Prostatic intraepithelial neoplasia and invasive prostatic adenocarcinoma in cystoprostatectomy specimens. Urology. 1989; 34(6 Suppl): 52-6.
16. Gleason D: Histologic grading and clinical staging of prostate carcinoma. In: Tannenbaum M (ed.), Urologic Pathology. The Prostate. Philadelphia, Lea & Febiger. 1977: pp. 171-97.
17. Chen ME, Johnston D, Reyes AO, Soto CP, Babaian RJ, Troncoso P: A streamlined three-dimensional volume estimation method accurately classifies prostate tumors by volume. Am J Surg Pathol. 2003; 27: 1291-301.
18. Crawford ED: Epidemiology of prostate cancer. Urology. 2003; 62(6 Suppl1): 3-12.
19. Nelson BA, Shappell SB, Chang SS, Wells N, Farnham SB, Smith JA Jr, et al.: Tumour volume is an independent predictor of prostate-specific antigen recurrence in patients undergoing radical prostatectomy for clinically localized prostate cancer. BJU Int. 2006; 97: 1169-72.
20. Pettaway CA, Troncoso P, Ramirez EI, Johnston DA, Steelhammer L, Babaian RJ: Prostate specific antigen and pathological features of prostate cancer in black and white patients: a comparative study based on radical prostatectomy specimens. J Urol. 1998; 160: 437-42.
21. Bastacky SI, Wojno KJ, Walsh PC, Carmichael MJ, Epstein JI: Pathological features of hereditary prostate cancer. J Urol. 1995; 153: 987-92.
22. Ray ME, Dunn RL, Cooney KA, Sandler HM: Family history of prostate cancer and relapse after definitive external beam radiation therapy. Int J Radiat Oncol Biol Phys. 2003; 57: 371-6.
23. Narod SA, Dupont A, Cusan L, Diamond P, Gomez JL, Suburu R, et al.: The impact of family history on early detection of prostate cancer. Nat Med. 1995; 1: 99-101.
24. Amling CL, Riffenburgh RH, Sun L, Moul JW, Lance RS, Kusuda L, et al.: Soderdahl DW, Donahue TF, Foley JP, Chung AK, McLeod DG. Pathologic variables and recurrence rates as related to obesity and race in men with prostate cancer undergoing radical prostatectomy. J Clin Oncol. 2004; 22: 439-45.
25. Rohrmann S, Roberts WW, Walsh PC, Platz EA: Family history of prostate cancer and obesity in relation to high-grade disease and extraprostatic extension in young men with prostate cancer. Prostate. 2003; 55: 140-6.

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EDITORIAL COMMENT

This study revealed no significant differences between patients with familial histories compared with the patients without familial histories of prostate cancer in relation their age, preoperative PSA, Gleason score, pathological stage, and surgical status of the margin. However, important data that could be answered is related to the disease-specific survival and biochemical disease-free survival. Otherwise, patients with familial PC had a larger volume of cancer per gland compared with the sporadic prostate cancer group - 3.3 cm^3 vs. 2.4 cm^3. This tumoral volume data justifies more attention for men with a familial history of prostate cancer, since the larger the tumoral volume, the larger the chances of biochemical recurrence. In cases of smaller tumoral volume (2.6 cc) normally the PSA is lower than 4.

REFERENCE

1. Zhu H, Roehl KA, Antenor JA, Catalona WJ: Biopsy of men with PSA level of 2.6 to 4.0 ng/mL associated with favorable pathologic features and PSA progression rate: a preliminary analysis. Urology. 2005; 66: 547-51.

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REPLY BY THE AUTHORS

We agree with the editorial comments by Dr. Dall'Oglio that it would be interesting to analyze any differences in the survival characteristics (biochemical-free survival and disease specific survival) of patients with sporadic prostate cancer compared to patients with a family history of prostate cancer. As discussed in the manuscript however, there is no convincing evidence to date that a positive family history impacts survival in those who have received therapy for clinically localized prostate cancer. Furthermore, we found no difference in tumor volume ($p = 0.27$) in patients with a positive family history of prostate cancer (1.72 cm3) vs. patients with sporadic prostate cancer (1.64 cm3) as demonstrated in Table 1. Bastacky and colleagues (reference #21 in the manuscript) found a non-statistically significant difference in the tumor volume of patients with familial prostate cancer compared to patients with sporadic prostate cancer (3.3 cm3 vs. 2.4 cm3).

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The Use of Immunohistochemistry for Diagnosis of Prostate Cancer

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ABSTRACT

Purpose: Atypical glands (ASAP) are diagnosed in 5.0% of prostate biopsies, and cancer identification in a rebiopsy is higher than 40.0%. The use of antibodies to mark basal cells is currently a common practice, in order to avoid rebiopsies. There has been no reported study that has reviewed characteristics of radical prostatectomies (RPs) when immunohistochemistry (IHC) was necessary for definitive diagnosis.

Materials and Methods: Out of 4127 biopsies examined from 2004 to 2008, 144 (3.5%) were diagnosed with ASAP. IHC was performed using antibody anti-34βE12 and p63. The results of surgical specimens of 27 patients treated by RP after the diagnosis of prostate cancer (PC) was made using IHC (Group 1) were compared with 1040 patients where IHC was not necessary (Group 2).

Results: IHC helped to diagnose PC in 103 patients (71.5%). Twenty-seven (26.2%) underwent RP. In Group 1, two (7.4%) adenocarcinomas were insignificant versus 29 (2.9%) for Group 2. Patients from Group 1 were younger ($p = 0.039$), had lower Gleason scores (GS) ($p < 0.001$), lower percentage of Gleason pattern 4 ($p < 0.001$), and smaller tumors ($p < 0.001$).

Conclusion: The use of IHC did not lead to diagnosis of insignificant tumors as illustrated by absence of differences in pathological stage or positive surgical margins in men submitted to RP. Therefore, our results suggest that this modality should be routinely used for a borderline biopsy and ASAP cases.

Key words: *prostatic neoplasms; diagnosis; biopsy; immunohistochemistry; atypical small acinar proliferation*
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INTRODUCTION

Atypical glands suspicious for carcinoma, also denominated atypical small acinar proliferation (ASAP), is not a specific entity but represents a large group of lesions which includes lesions that mimic cancer and, most importantly, carcinomas that lack all the cytological and/or architectural characteristics for the establishment of a definitive diagnosis of cancer. The frequency of this diagnosis is variable from 0.7 to 23.4%, with a mean of 5.0%, as reviewed by Epstein and Herawi (1). The possibility of diagnosing cancer in a subsequent biopsy is high, mean 40.2% (1-3). After radical prostatectomy (RP), the majority of cases are determined to be low grade and organ-confined (2,4,5).

In 1984, Gown and Vogel (6) reported the use of a monoclonal antibody anti-high molecular weight

cytokeratin (34βE12) to mark basal cells of the prostate that was later demonstrated as a characteristic of benign glands that retain the basal cell layer (7-9). In a larger series, Wojno and Epstein (10) used 34βE12 to diagnose adenocarcinoma in suspicious glands identified in needle prostate biopsies. Shah et al. (11) later proposed the combined use of p63, an homolog of the p53 tumor suppressor protein, as an auxiliary for the determination of cancer since it is also a protein expressed selectively by the basal cells of epithelial organs, including the prostate gland (12,13).

Recently, lower levels of prostate specific antigen (PSA) have been used to indicate the need for a prostate biopsy, and there has been an increasing number of cores taken in each biopsy session. These new practices have resulted in the representation of smaller tumors, often more adequately named ASAP. In addition, pathologists frequently use immunohistochemistry to enhance their diagnostic capabilities in order to avoid rebiopsies. There have been reports of false-positives and false-negatives for use of the combined 34βE12 and p63 cocktail. To date there has been no reported study that reviews surgical specimens of tumors from patients who underwent RP after a diagnosis of carcinoma in which the use of immunohistochemistry was necessary for the definitive diagnosis.

MATERIALS AND METHODS

From January 1st 2004 to July 31st 2008, 4127 biopsies were examined in our laboratory. ASAP was the diagnosis made for 144 (3.5%) of the biopsies. The mean age of the patients was 60.8 years old, median 60 ranging from 40 to 84 years old. Mean PSA was 7.11 ng/mL, with a median of 5.3 ng/mL, ranging from 1.4 to 43.5 ng/mL. The free to total relation of PSA was mean 15.1%, median 13.0%, ranging from 1 to 30%. The major reason for a biopsy among these patients was a progressive increase in PSA levels. One patient had a familiar history, and two had shown abnormalities in transrectal examination. In 31 patients (21.5%), ultrasound examination found abnormalities, hypoecoic and hypervascular areas. Twenty patients (13.9%) had previously undergone biopsies. The mean number of cores taken per biopsy session was 15.8, median 14, ranging from 6 to 40. All the slides were examined by the same uropathologist.

The immunohistochemistry was performed using a mouse monoclonal antibody anti-high molecular weight cytokeratin (clone 34βE12, Dako, Glostrup, Denmark) at a dilution of 1/100 and p63 (clone 4A4, Dako, Glostrup, Denmark) at a dilution of 1/100. After paraffin removal and hydration, the slides were immersed in 10 mM citrate buffer pH 6, for 15 min for antigen retrieval. The antibodies were incubated overnight at 4°C, and the secondary biotin-labeled antibody was incubated for 30 min at room temperature. The streptavidin labeled streptavidin-biotin amplification method (Dako K0679) was carried out for 30 minutes followed by peroxidase/diaminobenzidine substrate/chromagen. The slides were counterstained with hematoxylin.

RP was carried out in 27 out of 144 patients. The results were compared to 1040 patients who underwent RP during the same period and where the histology was sufficient to define adenocarcinoma. All patients were treated by the same group of surgeons. The surgical specimens were routinely examined in toto by the same pathologist. To measure tumor volume we used the grid method as described by Humphrey and Vollmer (14).

RESULTS

Immunohistochemistry permitted the definitive diagnosis of prostate cancer in 103 patients (71.5%) (Figure-1). The mean age of patients was 61.7 years old, median 61 (range 43 - 84); mean PSA was 7.6 ng/mL, median 5.4 ng/mL (range 1.4 - 44 ng/mL); and PSA free to total ratio was mean 15%, median 13% (range 1 - 29%). The mean Gleason score was 5.9, median 6 (range 4 to 7). The mean and median number of cores positive for tumor was 1.4 and 1 respectively, ranging from 1 to 4. The higher percentage of a single core that made up the tumor was mean 18.3%, median 10% (range 1 to 80%). The mean total percentage of tumor in all cores was 1.6%, median 1% (range 1 to 7%). Perineural invasion was not detected in any cases.

We had access to the surgical specimens from 27 (26.2%) patients who underwent radical prostatec-

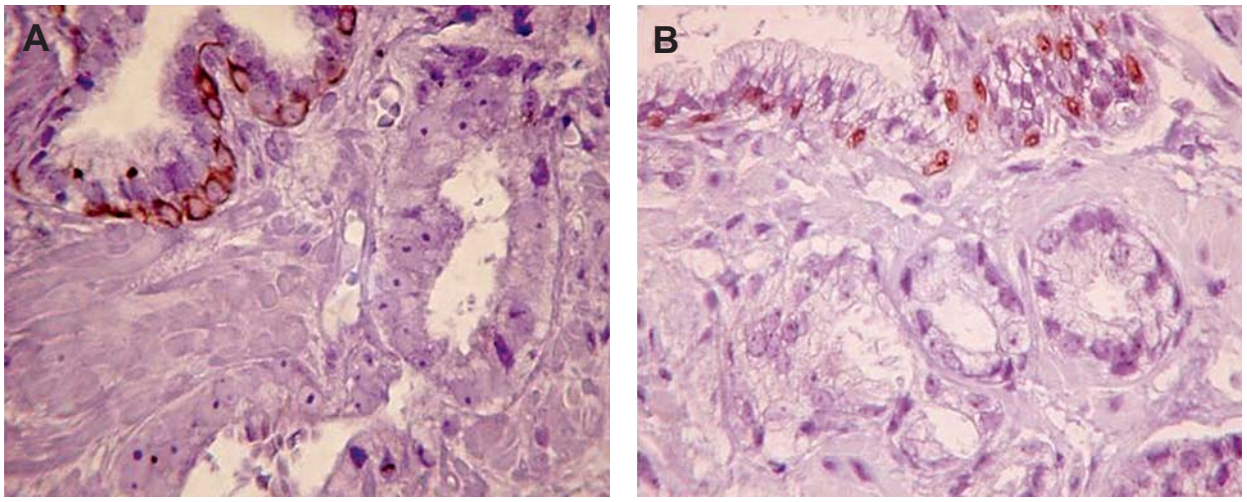

Figure 1 – *Immunohistochemistry study of prostate biopsy with atypical small acinar proliferation, where a diagnosis of adenocarcinoma was made because of the absence of basal cells in the neoplastic glands. A normal gland is represented at the top of the figure with basal cells stained by antibodies anti-high molecular weight cytokeratin 34βE12 (A) and anti-p63 (B).*

tomy. For the same period, from January 1 2004 to July 31 2008, 1040 patients also underwent radical prostatectomy after a diagnosis of adenocarcinoma that did not necessitate immunohistochemistry for the final diagnosis. The former will be referred to as Group 1, and the control group as Group 2. The characteristics of both groups are shown in Table-1. There were no pT0 in any of the two groups. Within Group

Table 1 – *Demographic description and tumor characteristics of patients submitted to radical prostatectomy for treatment of prostate cancer. Group 1 represents patients where immunohistochemistry was used for the definitive diagnosis. Group 2 represents patients where the diagnosis was made without any complementary study.*

	Group 1 (27)	**Group 2** (1040)	**p Value**
Age years old Median (Q1 - Q3)	56 (53 - 65)	61 (55 - 67)	0.039
Gleason Score Median (Q1 - Q3)	6 (6 - 6)	7 (6 - 7)	< 0.001
% of pattern 4 of Gleason Median (Q1 - Q3)	0 (0 - 17.75)	50 (9 – 100)	<0.001
Tumor volume % Median (Q1 - Q3)	3 (2.5 - 8.0)	11 (6 - 18)	<0.001
Stage pT2 pT3	 25 (92.6%) 2 (7.4%)	 824 (79.2%) 216 (20.8%)	 0.089
Positive surgical margins	6 (22.2%)	253 (24.3%)	0.801

1, two (7.4%) adenocarcinomas could be considered clinically insignificant, defined as less than 2% of the gland involved, organ-confined and with no Gleason 4 or 5 pattern present, versus 29 (2.9%) insignificant cases in Group 2 (15).

The patients in Group 1 were younger, had lower Gleason scores, a lower percentage of Gleason pattern 4 and smaller tumors. However, the rate of positive surgical margins was similar and there were no differences in pathological stage.

COMMENTS

The use of IHC as an auxiliary in the diagnosis of adenocarcinoma is a common practice in uropathology, and the use of antibodies against p63 and high molecular weight cytokeratin has been recommended as adjuncts in confirming prostatic carcinoma in doubtful cases.

Although basal cell markers, such as 34βE12 and p63 antibodies are useful for identifying basal cells, several benign mimickers of PC, such as atrophy, atypical adenomatous hyperplasia, nephrogenic adenoma, and mesonephric hyperplasia, can stain negatively with these markers. In addition, with patients being submitted to prostate biopsy with lower PSA levels and with larger numbers of cores being taken in each biopsy session, concern that patients are being overtreated is common.

Our results show that there was no overdiagnosis of PC with any pT0 after radical prostatectomy, with only 7.4% of cases classified as clinically insignificant. Tumor stage was similar for both groups, but only 7.4% of patients from Group 1 had stage pT3 tumors. On the other hand, positivity of surgical margins, a very important parameter related to the outcome of patients submitted to radical prostatectomy, mainly in organ-confined tumors (16,17), was similar for both groups; 22.2% and 24.3% in groups 1 and 2, respectively.

This is the first study to our knowledge to show histological characteristics of radical prostatectomy specimens in men submitted to surgery to treat adenocarcinoma where was necessary to use IHC for final diagnosis.

CONCLUSION

Our data show that the usage of IHC did not lead to diagnosis of insignificant tumors, as demonstrated by the study of the radical prostatectomy specimens that had similar pathological stage and positive surgical margins rates. Therefore, our results show that this modality should be routinely used to evaluate a borderline biopsy and ASAP cases.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Epstein JI, Herawi M: Prostate needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: implications for patient care. J Urol. 2006; 175: 820-34.
2. Leite KR, Mitteldorf CA, Camara-Lopes LH: Repeat prostate biopsies following diagnoses of prostate intraepithelial neoplasia and atypical small gland proliferation. Int Braz J Urol. 2005; 31: 131-6.
3. Schlesinger C, Bostwick DG, Iczkowski KA: High-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation: predictive value for cancer in current practice. Am J Surg Pathol. 2005; 29: 1201-7. Erratum in: Am J Surg Pathol. 2005; 29: 1548.
4. Hoedemaeker RF, Kranse R, Rietbergen JB, Kruger AE, Schröder FH, van der Kwast TH: Evaluation of prostate needle biopsies in a population-based screening study: the impact of borderline lesions. Cancer. 1999; 85: 145-52.
5. Iczkowski KA, Bassler TJ, Schwob VS, Bassler IC, Kunnel BS, Orozco RE, et al.: Diagnosis of "suspicious for malignancy" in prostate biopsies: predictive value for cancer. Urology. 1998; 51: 749-57; discussion 757-8.
6. Gown AM, Vogel AM: Monoclonal antibodies to human intermediate filament proteins. II. Distribution of filament proteins in normal human tissues. Am J Pathol. 1984; 114: 309-21.
7. Brawer MK, Peehl DM, Stamey TA, Bostwick DG: Keratin immunoreactivity in the benign and neoplastic human prostate. Cancer Res. 1985; 45: 3663-7.

8. Hedrick L, Epstein JI: Use of keratin 903 as an adjunct in the diagnosis of prostate carcinoma. Am J Surg Pathol. 1989; 13: 389-96.
9. O'Malley FP, Grignon DJ, Shum DT: Usefulness of immunoperoxidase staining with high-molecular-weight cytokeratin in the differential diagnosis of small-acinar lesions of the prostate gland. Virchows Arch A Pathol Anat Histopathol. 1990; 417: 191-6.
10. Wojno KJ, Epstein JI: The utility of basal cell-specific anti-cytokeratin antibody (34 beta E12) in the diagnosis of prostate cancer. A review of 228 cases. Am J Surg Pathol. 1995; 19: 251-60.
11. Shah RB, Zhou M, LeBlanc M, Snyder M, Rubin MA: Comparison of the basal cell-specific markers, 34betaE12 and p63, in the diagnosis of prostate cancer. Am J Surg Pathol. 2002; 26: 1161-8.
12. Barbareschi M, Pecciarini L, Cangi MG, Macrì E, Rizzo A, Viale G, et al.: p63, a p53 homologue, is a selective nuclear marker of myoepithelial cells of the human breast. Am J Surg Pathol. 2001; 25: 1054-60.
13. Signoretti S, Waltregny D, Dilks J, Isaac B, Lin D, Garraway L, et al.: p63 is a prostate basal cell marker and is required for prostate development. Am J Pathol. 2000; 157: 1769-75.
14. Humphrey PA, Vollmer RT: Percentage carcinoma as a measure of prostatic tumor size in radical prostatectomy tissues. Mod Pathol. 1997; 10: 326-33.
15. Guzzo TJ, Vira MA, Neway W, Hwang WT, Tomaszewski J, VanArsdalen K, et al.: Minimal tumor volume may provide additional prognostic information in good performance patients after radical prostatectomy. Urology. 2007; 69: 1147-51.
16. Psutka SD, Feldman AS, Rodin S, Wu CL, McDougal WS: Positive surgical margins do not affect recurrence in patients with T3a prostate cancer. J Urol. 2009; 181 (4Suppl): 776 #abstract 288.
17. Perez D, Shental J, Israel A, Salomon L, Abbou CC: Influence of positive surgical margins on adjuvant treatment after radical prostatectomy. J Urol. 2009; 181 (4 Suppl): 776 #abstract 2138.

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EDITORIAL COMMENT

Immunohistochemistry (IHC) for 34βE12 and p63 is at present a diagnostic standard for determining the presence of prostate cancer. It is also used to discriminate cancer from mimic cancer, when the definite diagnosis is difficult with conventional microscopic examinations; however, second biopsy is frequently recommended in practice. Indeed, 34 - 60% patients showing atypical small acinar proliferation (ASAP) in the primary biopsies were diagnosed with prostate cancer in repeat biopsy sessions (1,2).

As the authors stressed in the present paper, few studies have intentionally examined surgical specimens in patients with prostate cancer, who were primarily diagnosed with so-called atypical glands in previous biopsy specimens. Also, recent biopsy protocols such as multi-cores or saturation method has lead to an increase of ASAP (3). The authors elaborated patients' demographics as well as radical prostatectomy specimens, of which preoperative diagnosis in biopsy cores required 34βE12 and p63

IHC, to underscore the characteristics and outcome of this type of prostate cancer.

It is of interest that the patients in the IHC-required group were younger, had lower Gleason score and lower fraction with Gleason pattern 4, and had smaller tumor foci, compared with those in the IHC-unnecessary group. These facts may be relevant to lead-time bias in patients examined during different era with a different screening protocol, or simply based on earlier disease in younger patients. Although pathological T-stage and positive surgical margin rates were not statistically different between the two groups, the difference in patients' number between them possibly explains this contradiction. Also, the IHC-required group was considered to include good-risk cases, while the fraction of patients diagnosed with insignificant cancer was not large (7.4%). Positive surgical margin cases were distributed uniformly between the IHC-required and IHC-unnecessary groups, suggesting that 34βE12 and p63 IHC was useful as a preoperative diagnostics even for patients showing equivocal results in biopsy specimens with routine histology.

REFERENCES

1. Schlesinger C, Bostwick DG, Iczkowski KA: High-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation: predictive value for cancer in current practice. Am J Surg Pathol. 2005; 29: 1201-7. Erratum in: Am J Surg Pathol. 2005; 29: 1548.
2. Epstein JI, Herawi M: Prostate needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: implications for patient care. J Urol. 2006; 175: 820-34.
3. Ploussard G, Plennevaux G, Allory Y, Salomon L, Azoulay S, Vordos D, et al.: High-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation on initial 21-core extended biopsy scheme: incidence and implications for patient care and surveillance. World J Urol. 2009; 27: 587-92.

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EDITORIAL COMMENT

This study was carried out in order to investigate the value of immunohistochemstry (IHC) in borderline pathological prostate cancer cases. Immunostaining has gained an important role in the evaluation of borderline biopsy cases, especially when high-grade prostate intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP) are present. The predictive values of ASAP and HPGIN for cancer detection on repeat biopsies are 39 and 23%, respectively (1). Usually, the presence of ASAP in the initial biopsy tissue requires re-biopsy within 6-12 months considering other clinical features (age, comorbidities etc.). Although this topic has not been sufficiently discussed in the literature, it may have a significant impact on patient management. It has been previously recommended that a second biopsy should include extensive sampling of the initial atypical site as well as adjacent ipsilateral and contralateral sites with routine extended schemes. However, extensive transrectal sampling may increase the risk of infection (2). Herein the authors demonstrate that imunohistochemical approach, using monoclonal antibody anti-high molecular weight cytokeratin and p63, may assist in a more accurate diagnosis of ASAP and, therefore, may obviate the need for re-biopsies with the potential complications. The main benefit from this study should be related to diagnosis and pretreatment judgment.

This study shows comparable tumor stage in both study groups (radical prostatectomy after IHC diagnosis and control) and recommends the inclusion of IHC in ASAP cases work-up.

This study contributes to our daily clinical practice and may have major impact on our judgment in borderline prostate biopsy cases. Similar studies evaluating novel methods to enhance biopsy-based diagnosis accuracy should be encouraged in view of the intriguing concept of active surveillance. This study also leads to a yet another question - does active or passive surveillance miss cases of significant tumors that should be treated more aggressively? Future studies are warranted to answer this question.

REFERENCES

1. Iczkowski KA: Current prostate biopsy interpretation: criteria for cancer, atypical small acinar proliferation, high-grade prostatic intraepithelial neoplasia, and use of immunostains. Arch Pathol Lab Med. 2006; 130: 835-43.
2. Epstein JI, Herawi M. Prostate needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: implications for patient care. J Urol. 2006; 175: 820-34.

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EDITORIAL COMMENT

Authors compared the pathologic stage between radical prostatectomy cases performed in patients for which cancer was diagnosed with the help of combined 34βE12 and p63 cocktail IHC (n = 27) or not (n = 1040). Their results showed that there was no overdiagnosis of prostate cancer with any stage pT0 after radical prostatectomy, with only 7.4% of cases classified as clinically insignificant. This shows the interest of IHC staining and the quality of the pathologist reading.

Pathologists frequently use immunohistochemistry to enhance their diagnostic capabilities in order to avoid rebiopsies in cases of diagnosis difficulty, which is a frequent situation in biopsy reading. I would make 2 comments:

1) Recent studies recommend not to use the ASAP definition but atypical foci
2) It was also demonstrated that a different IHC of a p63/alpha-methyl-CoA-racemase (p504s) cocktail in case of atypical foci in the prostate has a diagnostic utility (1-3).

Authors did not use this p504s in their IHC study. It may be discussed whether the addition of the p504s is superior or not to the 34βE12 and p63 cocktail authors used.

REFERENCES

1. Molinié V, Fromont G, Sibony M, Vieillefond A, Vassiliu V, Cochand-Priollet B, et al.: Diagnostic utility of a p63/alpha-methyl-CoA-racemase (p504s) cocktail in atypical foci in the prostate. Mod Pathol. 2004; 17: 1180-90.
2. Iczkowski KA, MacLennan GT, Bostwick DG: Atypical small acinar proliferation suspicious for malignancy in prostate needle biopsies: clinical significance in 33 cases. Am J Surg Pathol. 1997; 21: 1489-95.
3. Iczkowski KA: Current prostate biopsy interpretation: criteria for cancer, atypical small acinar proliferation, high-grade prostatic intraepithelial neoplasia, and use of immunostains. Arch Pathol Lab Med. 2006; 130: 835-43.

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REPLY BY THE AUTHORS

To Dr. Arnauld Villers Comment

ASAP is a term that has been discussed in uropathology meetings, and some pathologists argument that the suspicious gland is not always small, so it should be called atypical focus. ASAP was a very good term coined to describe doubtful lesions, and has been used for a long time. It means for us, pathologists, the presence of a small focus of atypical glands, not necessarily small, highly suspicious for cancer and help pathologists and urologists to communicate. Also, used as a keyword facilitates the search in the literature, whereas atypical has a profuse meaning. Concerning the use of alpha-methyl-CoA-racemase (p504s), it has been shown that it stains number of benign prostate glands, periurethral glands and mimics of prostate cancer (1), increases the cost and help the final decision in only 50% of cases (2).

REFERENCES

1. Gologan A, Bastacky S, McHale T, Yu J, Cai C, Monzon-Bordonaba F, Dhir R: Age-associated changes in alpha-methyl CoA racemase (AMACR) expression in nonneoplastic prostatic tissues. Am J Surg Pathol. 2005; 29: 1435-41.
2. Zhou M, Aydin H, Kanane H, Epstein JI: How often does alpha-methylacyl-CoA-racemase contribute to resolving an atypical diagnosis on prostate needle biopsy beyond that provided by basal cell markers? Am J Surg Pathol. 2004; 28: 239-43.

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Penile Prosthesis Implantation in an Academic Institution in Latin America

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ABSTRACT

Purpose: We performed a retrospective study to analyze the effectiveness of implantable penile prostheses in the treatment of erectile dysfunction.
Materials and Methods: This study included 249 patients who received implants between 2001 and 2008. A total of 139 patients who underwent penile prosthesis implantation were interviewed.
Results: Approximately half of patients had previously used oral drugs before implantation of the prosthesis. About 45% had diabetes, 25.9% had previously undergone radical prostatectomy (RP), and 64% had hypertension. Exchange was performed in 5.7% for fracture, inadequate size, or extrusion. A total of 24.5% of men had immediate postoperative pain, 7.9% had local infection, and 8.6% had other complications. Patients who had previously undergone RP were 3.2 times more likely to experience a postoperative complication than patients who had not ($p = 0.061$). Eighty-nine (64%) patients returned to having sex as they had before being diagnosed with ED. Ninety-two of the men (66.2%) had sexual intercourse one to two times per week. One hundred twenty patients (86.3%) rated their level of satisfaction as good, excellent or very good, which was similar to the percentage of partners. The mean follow-up was 40 months.
Conclusion: Higher rates of postoperative infections and mechanical problems with the implant were found in this study as compared to other studies, which was probably associated with the relative lack of experience of the trainees who were performing the surgeries. Patients with a history of RP or diabetes mellitus prior to implantation were at higher risk of postoperative complications.

Key words: *penile prosthesis; erectile dysfunction; educational institution; impotence*
Int Braz J Urol. 2010; 36: 591-601

INTRODUCTION

Currently, there are three options that are frequently used to treat erectile dysfunction (ED). The first is the use of oral drugs, especially phosphodiesterase-5 (PDE-5) inhibitors. These drugs are easy to use and widely accepted. The second option is the intra-cavernous injection (IC) of vasoactive drugs. The third option, which is most often used when the other two options fail or cannot be used, is the use of implantable penile prostheses (1). It is a definitive treatment for ED in most cases.

In patients with hypertension, PDE-5 inhibitors are very effective and tolerable, but when there are failures in this treatment the best option remains the implantation of penile prosthesis. In patients undergoing hemodialysis, or who have recurrence of prostate cancer after radiation therapy and are undergoing

surgery, with poor response to oral medications, the prosthesis is a good treatment option (2-4).

The contemporary history of implants of prostheses began in the 1970s. With the technical improvement of the prosthesis, there was a marked decrease in the number of complications and revision surgeries that patients experienced, thereby increasing the popularity and use of this therapeutic option (5,6). Today, there are over 30,000 penile prostheses implanted per year, with most of these surgeries being performed in North America (4).

Although the implantation of penile prostheses is fairly common, our knowledge about patients' psychological and personal aspects experiences are limited (7,8).

The main goals of this study were to examine the effectiveness of implantable penile prostheses, the complications associated with this surgery, and its acceptance by patients who were treated at an academic institution, as well as to compare these results with data available in the literature.

MATERIALS AND METHODS

This was a retrospective study of 249 patients who underwent surgery for the implantation of penile prostheses between 1998 and 2009 at an academic institution: the University of São Paulo Medical School in Brazil.

The criteria for inclusion in the study were erectile dysfunction (ER) that was refractory to treatment with oral medications or IC injections, present within normal examinations range in the preoperative period, both on the biochemical and cardiovascular assessments which was confirmed prior to implantation of the prosthesis. The demographics and the follow-up data were taken from electronic medical records of the division of urology.

The urology residents at our institution complete a three-month rotation in sexual dysfunction during their training. The mean number of surgeries performed during each rotation was 21 surgeries per trainee. Thus, in this study, the surgeries were performed by different residents during the course of the study.

These patients were implanted inflatable prosthesis fittings and three volumes. In the vast majority, 137 patients had the implant prosthesis fittings for having a lower cost and being performed in a public hospital. There was the implantation of two inflatable prostheses that were received as a donation for demonstrative surgery. The mark of a malleable prosthesis was variation; they depended on purchases based on a price found at the time of purchase.

The patients received a single dose of antibiotics (500 mg of ciprofloxacin) on the day of surgery. In the operating room, the surgical site was carefully prepped and draped in a sterile fashion. Local or regional anesthesia was used most often, but, if necessary, general anesthesia was used. In the postoperative period, patients had a urethral catheter left in for bladder drainage for 24 hours and were given additional doses of ciprofloxacin for antibiotic coverage.

The technique used to implant the cylinders of the prosthesis was similar in all cases. The stents were placed after expansion of the corpus cavernosum, careful size measurement, and thorough irrigation of the operative field with saline solution containing 80 mg of gentamycin. The corpus cavernosum was closed with 3-0 Vicryl sutures in most cases. In other patients, a wire is used for closure, which was not absorbable. The mean surgical time was 2 hours. Teaching urologists with more experience in placing implants were present during all surgeries. Patients were discharged from the hospital the day after surgery, after removal of the urethral catheter, and were counseled to take seven days of oral antibiotics after discharge.

Patients were given recommendations regarding postoperative care, the resumption of sexual activity, and return appointments for outpatient follow-up.

We contacted all patients who underwent implantation of prosthesis between January 1998 and May 2009, a total of 249 patients. Of this number, 139 patients agreed to be interviewed personally about their experience with the surgery. They were asked questions regarding the immediate postoperative period (i.e., whether or not they experienced pain, infection, or other local complications) as well as questions regarding the use of the prosthesis during sexual activity (i.e., time to resumption of sexual activity, whether sex was normal or not the same after prosthesis implantation, their use of lubricants, and

the frequency of their sexual activity). We also analyzed the complications (wound dehiscence, urinary problems, or local secretions) that occurred both in the immediate postoperative period and at a later time. Patients' personal satisfaction with the prosthesis, as well as the satisfaction of their partner, was queried, and patients were asked whether or not they would choose to undergo the surgery again.

We used the chi-square test to examine the relationship between postoperative complications and various clinical and demographic characteristics. Unconditional logistic regression models were used to examine the association between these characteristics and patients' risk of postoperative complications and calculated odds ratios and 95% confidence intervals. Statistical analyses were performed using SPSS 12.0 (SPSS Inc., Chicago, IL, USA) for Windows and significance was set as $p < 0.05$.

RESULTS

We included 139 patients who underwent prosthesis implantation in our study. An additional 110 patients who underwent surgery during the same time period failed to contact. The mean follow-up time of included patients was 40 months (range: 7 to 139 months). The median follow-up time was 35 months.

The median age of included patients was 63 years. One hundred and sixty-eight (92.1%) patients were white. The level of schooling was the same: illiterate 1 (0.7%); elementary in 22 (15.8%); middle school 54 (38.8%), medium full 15 (10.8%) high school 4 (2.9%); undefined 43 (30.9%).

Of these patients, 18 (13%) had no fixed partner. Seventy-three patients (52.5%) had used oral medication for ED before surgery, and forty-four (31.7%) had used IC injections.

Regarding medical comorbidities, 63 patients (45.3%) reported diabetes mellitus. Thirty-six patients (25.9%) had previously undergone radical prostatectomy (RP) for prostate cancer and had PSA values that indicated that they had non-recurrent disease. Eighty-nine patients (64.0%) had hypertension. Thirty patients (21.5%) patients had cardiovascular disease. Five patients (3.6%) had spine or spinal cord pathology. These data are shown in Table-1.

Table 1 – *Demographic data of 139 patients undergoing penile prosthesis implantation surgery.*

Age (years) - mean ± standard deviation, range	62.68 ± 9.96, 34-83
White race	128 (92.1%)
Schooling	
Illiterate	1 (0.7%)
Basic incomplete	22 (15.8%)
Basic completed	54 (38.8%)
Middle completed	15 (10.8%)
Superior completed	4 (2.9%)
Not defined	43 (30.9%)
Partner marriage	121 (87.1%)
Previous use of oral medications	73 (52.5%)
Previous use of intra-cavernous injections	45 (32.4%)
Diabetes mellitus	63 (45.3%)
Previous radical prostatectomy	36 (25.9%)
Hypertension	89 (64.0%)
Cardiovascular disease	30 (21.6%)
Spine/spinal cord pathology	5 (3.6%)
Peyronie's disease	9 (6.5%)

***Table 2** – Immediate and long-term complications of 139 patients who underwent penile prosthesis implantation surgery.*

Postoperative pain	34 (24.5%)
Infection in the immediate postoperative period	11 (7.9%)
Various other complications*	12 (8.6%)
Fracture of the prosthesis	5 (3.6%)
Withdrawal/exchange of prosthesis	12 (8.6%)
Withdrawal due to ineffectiveness	4 (2.9%)
Exchange due to fracture	2 (1.4%)
Exchange due to size inadequacy	4 (2.9%)
Exchange due to cylinder extrusion	2 (1.4%)

**Wound dehiscence, voiding difficulty, local secretions without infection.*

Of the 139 patients interviewed, only 2 had inflatable prostheses placed in three volumes, because this is a prosthesis of high cost, only the placements were made in those patients who received these implants as a gift from supplier, to perform a surgical demonstration. In terms of late complications, 12 (8.6%) patients had to undergo revision surgery, of whom, 4 (2.9%) had the prosthesis removed due to inefficacy and 8 (5.7%) had their prostheses exchanged. Of the eight patients requiring the exchange of prostheses, two (1.4%) required an exchange of prosthesis due to fracture, four (2.9%) due to inadequate size, and two (1.4%) patients had to undergo prosthesis exchange due to extrusion of the cylinder. In presenting extrusion, when the placement of new indentures was made to strengthen local Dacron, we found three (2.2%) patients who had experienced prosthetic fracture without knowledge of the problem and had normal sexual function.

In the immediate postoperative period, 34 (24.5%) patients reported having pain, 11 (7.9%) had local infections and 12 (8.6%) had other complications (wound dehiscence, difficulty voiding, or local secretions without infection), as shown in Table-2.

The results of the univariate analysis of the relationship between postoperative complications and patient characteristics, previous medication use, and medical comorbidities are shown in Table-3.

Based on Table-3, it can be observed that none of the variables analyzed were statistically significantly associated with risk of postoperative complications ($P > 0.05$). However, a marginally significant association was observed between history of RP and post-operative complications ($P = 0.061$). Patients who had previously undergone RP had a 3.2 times higher risk of complications than patients who had not undergone RP. Despite the fact that we found no statistically significant associations between risk of complications and the patient characteristics listed in Table-3 on univariate analysis, we created a multivariate model that included all variables with $P < 0.20$ to further investigate the association between these variables and postoperative complications.

We included age, diabetes, and history of RP in the multivariate model. We found that that age was not independently associated with postoperative complications ($P = 0.483$), but that prior history of RP was significant ($P = 0.029$) and prior history of diabetes was marginally significant ($P = 0.072$) associated with postoperative complications. Despite the marginally significant association between diabetes and postoperative complications, it was kept in the model because when it was removed, history of RP was no longer significantly associated with postoperative complications. In other words, RP was independently associated with postoperative complications only when the model was adjusted for diabetes status. The risk of postoperative complications among patients with prior RP was 3.3 times higher than that

Table 3 – *Distribution of postoperative complications based on clinical characteristics of patients undergoing surgery for implantation of a penile prosthesis.*

	Postoperative Complications				
	Yes (N = 12)	**No** (N = 127)	**Odds Ratio**	**95% CI**	**p Value**
Age (years)			1.048	[0.979; 1.121]	0.179
Mean ± SD	66.5 ± 7.5	62.5 ± 10.1			
Range	55-80	34-83			
White race					0.264
No	2 (16.7%)	9 (7.2%)	2.578	[0.489;13.595]	
Yes	10 (83.3%)	116 (92.8%)			
PDE-5 inhibitors					0.337
Yes	8 (66.7%)	65 (52.0%)	1.846	[0.529;6.447]	
No	4 (33.3%)	60 (48.0%)			
IC injections					0.970
Yes	4 (33.3)%	41 (32.8%)	1.024	[0.291;3.600]	
No	8 (66.7%)	84 (67.2%)			
Diabetes mellitus	8 (66.7%)	55 (44.0%)	2.545	[0.728;8.894]	0.143
	4 (33.3%)	70 (56.0%)			
Yes					
No					
RP					0.061
Yes	6 (50.0%)	30(24.0%)	3.167	[0.950;10.553]	
No	6 (50.0%)	95 (76.0%)			
Hypertension					0.897
Yes	8 (66.7%)	81 (64.8%)	1.086	[0.310;3.811]	
No	4 (33.3%)	44 (35.2)%			
CVD					0.648
Yes	2 (16.7%)	28 (22.4%)	0.693	[0.143;3.348]	
No	10 (83.3%)	97 (77.6%)			

CVD = cardiovascular disease; IC = intra-cavernous injection; RP = radical prostatectomy.

observed among patients without prior RP (95% CI = 1.150, 14.390, P = 0.029).

Of the 139 patients studied, the median time to return to sexual activity was 6 weeks (range: 1 to 20 weeks). Eighty-nine (64%) patients returned to having sex as they had previously, that is, restored to a number of sexual intercourses per week in numbers equal to or greater than they had before submitting the framework of ED, which led them to do the surgery, where as sixty-eight (48.9%) used lubricants. Ninety-two patients (66.2%) had a sexual frequency of one to two times per week. Regarding personal satisfaction for the results obtained after the implantation of the prosthesis, 120 patients (86.3%) rated their level of satisfaction as good, excellent, or very good. Patients' partners had similar levels of satisfaction (83.4% rated their level of satisfaction as good, very good, or excellent). These data are shown in Table-4.

Table 4 *– Sexual function and satisfaction after surgery among 139 patients who underwent implantation of a penile prosthesis.*

Mean time to return to sex	6.0 weeks
Range	1 - 20 weeks
Normal sex	89 (64.0%)
Use of a lubricant	68 (48.9%)
Weekly frequency of sexual activity	
< 1 time	26 (18.7%)
> 4 times	1 (0.7%)
1 to 2 times	92 (66.2%)
3 to 4 times	20 (14.4%)
Patient satisfaction with the prosthesis	120 (86.3%)
Sexual partners' satisfaction with the prosthesis*	101 (83.5%)
Would undergo the surgery again	123 (88.5%)

**Based on the responses of 121 partners.*

COMMENTS

After the failure of oral drugs and intra-cavernous injections, the placement of a penile prosthesis is the final option for patients with ED (9-11). The safety and effectiveness of penile prostheses has previously been demonstrated in numerous studies (12-14).

After collecting data regarding the placement of penile prostheses by several surgeons at our academic center, we analyzed the data to examine the effectiveness of implantable penile prostheses as well as the complications associated with them.

Meticulous technique and experience are important in most surgeries, but are especially important for penile prosthesis implantation. Previous studies have demonstrated that the patients who underwent implantation of a penile prosthesis for the first time have a lower risk of complications than patients undergoing a second implantation surgery due to a complication, such as extrusion of prostheses, infection, or inadequacy of the device. Many studies regarding the implantation of penile prosthesis have emphasized the importance of success with the first surgery because surgical revision is associated with a worse prognosis and higher rate of complications. (15-18).

The rates of infection in repeat surgeries tend to be higher than those for the initial implantation surgery. The postoperative infection rate in our series was 7.9%, which is much higher than has been found in most previous studies. Jarow (19) reported an infection rate of 1.8% after the primary surgery and Govier et al. (20) reported a rate of 2.1%.

Finally, it is possible that some component of bad preparation materials occurred in our surgery center that had increased this rate to a higher level.

Infection leads to damage in the smooth muscle of the corpus cavernosum and leads to scarring. This may also lead to a shortening of the penis and increase the difficulty of placing another prosthesis in the future (21). The vast majority of infections occur within the first year after implantation (22).

The explanation for a higher rate of infections such as that found in this study may be related to several factors, such as the limited experience of medical trainees who have to perform these surgeries, the short time that the residents are in the group of sexual medicine, which perform these surgeries, the high number of surgeries in the operating room of our hospital, which is one of the busiest in the city of Sao Paulo, the economic and social conditions of patients undergoing these surgeries, and may therefore have a higher susceptibility to infections or low

nutritional level than by careless personal hygiene during the postoperative period, which as we know it is extremely important.

The fact that residents have a relatively short period of training with the group of attending surgeons who perform implant prostheses means that they do not obtain the experience necessary to perfect their surgical technique, possibly resulting in a higher infection rate. The learning curve for the implantation of prostheses is likely greater than the number of surgeries each resident performed in this study.

Another factor that may be associated with the high number of infections in these surgeries is the large number of people that move in and out of the operating rooms at our hospital, which is explained by the fact that our center is a high-volume academic center that has a number of residents that participate in various surgeries.

Based on the results of this study, it is clear that there is a need for a more thorough and comprehensive analysis of all of the factors that influence infection rates as well as a need to establish an optimal number of penile prosthesis implantation surgeries that should be performed during residency training in order to improve the educational experience and technical skills of urology residents.

When we examined the factors we thought might be related to post-operative infections among these 139 patients, we found no significant relationship between risk of infection and medical comorbidities. This may be explained by the higher level of preoperative care that is generally provided at academic institutions, which includes subspecialty care and an integrated approach to care between multiple subspecialties.

Regarding the survival rate of penile prostheses, malleable prostheses are associated with lower rates of mechanical problems than inflatable prostheses, due to the simplicity of their design. Lotan et al. found that the rate of survival (without technical problems) of malleable prosthesis was 87% as compared to 50% for inflatable prostheses (15). There is an increased likelihood of mechanical problems with inflatable prostheses (as compared to malleable prostheses), which is directly related to the greater complexity of these implants (23). In our series, the two patients who received inflatable prostheses of three pieces did not experience any complications.

Our rate of mechanical problems with implanted prostheses was 3.59%. Atienza (24) analyzed 52 articles indexed in Medline that were related to this topic and found a 1.4% overall rate of mechanical problems, i.e., breaks in semi-rigid prostheses, in these studies. This difference could be explained by the increased handling of the prosthesis at the time of implantation that occurred in our series, given that all surgeries were performed by medical residents.

Atienza also found 7.1% rate of exchange or withdrawal of prosthesis, which was similar to our study, in which we observed a rate of 8.63%. Of these, most exchanges were performed due to inadequate cylinder size. Interestingly, we found three patients (2.15%) who had a fracture of the prosthesis without being aware of the problem, all of whom had normal sexual activity. This complication was not included in the complication rate indices described in the literature.

The immediate postoperative complication rates in our series were also higher than those found in other centers, but the significance of these issues was minimal, such as minor wound dehiscence and local, low-volume, non-purulent secretion. The differences in these complication rates are most likely explained by differences in the preoperative care and the preparation of patients in the operating room.

Regarding diabetes, several studies have shown no correlation between the presence of this disease and infection after surgery (25-27).

On multivariate analysis, the presence of diabetes mellitus and radical prostatectomy were both found to have a marginally significant association with higher rates of post-operative complications. The most likely explanation for the association of these diseases with postoperative complications is a disruption in the corpus cavernosum and the penile vasculature. Of note, we only considered patients for surgery whose glucose levels remain stable below 150 mg/dL.

Patients and their partners seemed, overall, to be satisfied with the prostheses. A total of 86.3% of men and 84.2% of partners were satisfied with the results of surgery. Most men had sex more than two times per week (81.3%). These numbers are very encouraging, especially given that prostheses were

generally the only possible method of treatment left to attempt to treat ED in these patients.

Regarding the few patients who were dissatisfied with the prosthesis, the dissatisfaction appeared to be related to a feeling of unnatural sexual relations. This is because with the prosthesis, foreplay is no longer necessary for the start of erection (3) Patient dissatisfaction may also be related to delayed ejaculation, which is a possible side effect of the implant, and was observed in some patients in this study.

We also saw that the patient dissatisfaction seemed to lead to partner dissatisfaction (26). The dissatisfaction of partners may also be related to the fact that, for some partners, the sexual experience does not fully meet the expectations that they had prior to the time of surgery. These unrealistic expectations probably reflect a lack of appropriate counseling prior to surgery (28-30).

One factor that could have a large influence on the satisfaction rates of men and their partners, which was found in our study and has been commented on in the literature (31-33), can be attributed to the fact that the interviews were not performed separately. This could have allowed the partner to express his/her opinion about the prosthesis more freely and openly. This hypothesis is in agreement with other studies, which found lower partner satisfaction levels when wives were interviewed separately from their husbands (34,35).

It is very important to obtain high levels of patient and partner satisfaction after penile prosthesis implantation surgery. In order to obtain high levels of satisfaction, explanation of the surgery, the possible complication associated with it, and the use of prostheses must be made repeatedly when patients with indications for the placement of prostheses are seen in our clinic. The use of lubricants also appears to improve patient satisfaction, because its use prevents the discomfort caused by initial sexual activity after implantation, and patients should also be counseled regarding this.

One of the limitations of this study was that it was performed retrospectively, leading normal shortcomings of retrospective studies in which patients cannot remember very well all the issues that arose following the surgery, or intensity. Another limitation was the lack of knowledge about the use of this method to treat ED by patients who have little education and knowledge.

CONCLUSIONS

We found that at our academic institution, penile prosthesis implantation was an effective treatment method for patients with ED who had difficulty using or who did not benefit from other ED treatments. There was a high rate of patient and partner satisfaction associated with this surgery. Higher rates of postoperative infections and mechanical problems were found in this study than in other studies, which is probably associated with the relatively low experience level of the residents who performed the surgery.

Additionally, a history of radical prostatectomy and diabetes mellitus prior to implantation are considered in the risk factors for postoperative complications.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Yildirim A, Basok EK, Basaran A, Tokuc R: Gangrene of the distal penis after implantation of malleable penile prosthesis in a diabetic patient. Adv Ther. 2008; 25: 143-7.
2. Dall'Oglio MF, Barreto F, Paranhos M, Nesrallah A, Nesrallah L, Srougi M: Salvage radical prostatectomy: an alternative treatment for local recurrence of radioresistant cancer. Int Braz J Urol. 2006; 32: 550-6.
3. Messina LE, Claro JA, Nardozza A, Andrade E, Ortiz V, Srougi M: Erectile dysfunction in patients with chronic renal failure. Int Braz J Urol. 2007; 33: 673-8.
4. Albuquerque DC, Miziara LJ, Saraiva JF, Rodrigues US, Ribeiro AB, Wajngarten M: Efficacy, safety and tolerability of sildenafil in Brazilian hypertensive patients on multiple antihypertensive drugs. Int Braz J Urol. 2005; 31: 342-53; discussion 354-5.

5. Conde JL, Saens A, Imaz I. Efectividad y seguridad de las protesis de pene. avaliable at in: http://www.isciii.es/htdocs/investigacion/publicaciones_agencia/15ProtesisPene.pdf
6. Lewis, R: Surgery for Erectile Dysfunction. In: Walsh PC, Retik AB, Vaughan ED, Wein AJ (eds.), Campbell's Urology. Philadelphia. WB. Saunders Co. 1998; pp. 1215.
7. Robles VC, Gonzales LL, Mateo CP, Castro GE, Cagigal IR, Sanchez AB. Protesis de pene. Resultado de calidad y morbidad. Arch. Esp.Urol. 2005; 58: 925-30.
8. Salama N: Satisfaction with the malleable penile prosthesis among couples from the MiddLe East--is it different from that reported elsewhere? Int J Impot Res. 2004; 16: 175-80.
9. Burns-Cox N, Burston A, Gingell JC: Fifteen years experience of penile prosthesis insertion. Int J Impot Res. 1997; 9: 211-6.
10. Levine LA, Estrada CR, Morgentaler A: Mechanical reliability and safety of, and patient satisfaction with the Ambicor inflatable penile prosthesis: results of a 2 center study. J Urol. 2001; 166: 932-7.
11. Fagelman E, Fagelman A, Shabsigh R: Efficacy, safety, and use of sildenafil in urologic practice. Urology. 2001; 57: 1141-4.
12. Baniel J, Israilov S, Segenreich E, Livne PM: Comparative evaluation of treatments for erectile dysfunction in patients with prostate cancer after radical retropubic prostatectomy. BJU Int. 2001; 88: 58-62.
13. Wilson SK, Cleves M, Delk JR 2nd: Long-term results with Hydroflex and Dynaflex penile prostheses: device survival comparison to multicomponent inflatables. J Urol. 1996; 155: 1621-3.
14. Daitch JA, Angermeier KW, Lakin MM, Ingleright BJ, Montague DK: Long-term mechanical reliability of AMS 700 series inflatable penile prostheses: comparison of CX/CXM and Ultrex cylinders. J Urol. 1997; 158: 1400-2.
15. Lotan Y, Roehrborn CG, McConnell JD, Hendin BN: Factors influencing the outcomes of penile prosthesis surgery at a teaching institution. Urology. 2003; 62: 918-21.
16. Govier FE, Gibbons RP, Correa RJ, Pritchett TR, Kramer-Levien D: Mechanical reliability, surgical complications, and patient and partner satisfaction of the modern three-piece inflatable penile prosthesis. Urology. 1998; 52: 282-6.
17. Dubocq F, Tefilli MV, Gheiler EL, Li H, Dhabuwala CB: Long-term mechanical reliability of multicomponent inflatable penile prosthesis: comparison of device survival. Urology. 1998; 52: 277-81.
18. Henry GD, Kansal NS, Callaway M, Grigsby T, Henderson J, Noble J, et al.: Centers of excellence concept and penile prostheses: an outcome analysis. J Urol. 2009; 181: 1264-8.
19. Jarow JP: Risk factors for penile prosthetic infection. J Urol. 1996; 156: 402-4.
20. Govier FE, Gibbons RP, Correa RJ, Pritchett TR, Kramer-Levien D: Mechanical reliability, surgical complications, and patient and partner satisfaction of the modern three-piece inflatable penile prosthesis. Urology. 1998; 52: 282-6.
21. Montague DK, Angermeier KW: Penile prosthesis implantation. Urol Clin North Am. 2001; 28: 355-61.
22. Sadeghi-Nejad H: Penile prosthesis surgery: a review of prosthetic devices and associated complications. J Sex Med. 2007; 4: 296-309. Erratum in: J Sex Med. 2007; 4: 1520.
23. Montague DK, Barada JH, Belker AM, Levine LA, Nadig PW, Roehrborn CG, et al.: Clinical guidelines panel on erectile dysfunction: summary report on the treatment of organic erectile dysfunction. The American Urological Association. J Urol. 1996; 156: 2007-11.
24. Atienza Merino G: Penile prosthesis for the treatment of erectile dysfunction. Actas Urol Esp. 2006; 30: 159-69.
25. Wilson SK, Carson CC, Cleves MA, Delk JR 2nd: Quantifying risk of penile prosthesis infection with elevated glycosylated hemoglobin. J Urol. 1998; 159: 1537-9; discussion 1539-40.
26. Montague DK: Periprosthetic infections. J Urol. 1987; 138: 68-9.
27. Carson CC: Complications of penile prostheses and conmplex implantations. In: Carson CC, Kirby RS, Goldstein I (ed.), Textbook of Erectile Dysfunction. Isis Medical Media, Oxford. 1999, pp. 435-50.
28. McLaren RH, Barrett DM: Patient and partner satisfaction with the AMS 700 penile prosthesis. J Urol. 1992; 147: 62-5.
29. Krauss DJ, Lantinga LJ, Carey MP, Meisler AW, Kelly CM: Use of the malleable penile prosthesis in the treatment of erectile dysfunction: a prospective study of postoperative adjustment. J Urol. 1989; 142: 988-91.

30. Montorsi F, Guazzoni G, Bergamaschi F, Rigatti P: Patient-partner satisfaction with semirigid penile prostheses for Peyronie's disease: a 5-year followup study. J Urol. 1993; 150: 1819-21.
31. Furlow WL, Barrett DM: Inflatable penile prosthesis. New device design and patient-partner satisfaction. Urology. 1984; 24: 559-63.
32. Beutler LE, Scott FB, Karacan I, Baer PE, Rogers RR Jr, Morris J: Women's satisfaction with partners' penile implant. Inflatable vs noninflatable prosthesis. Urology. 1984; 24: 552-8.
33. Fallon B, Ghanem H: Sexual performance and satisfaction with penile prosthesis in impotence of various etiologies. Int J Impot Res 1990; 2: 35-42.
34. Schover LR, von Eschenbach AC: Sex therapy and the penile prosthesis: a synthesis. J Sex Marital Ther. 1985; 11: 57-66.
35. Tiefer L, Pedersen B, Melman A: Psychosocial follow-up of penile prosthesis implant patients and partners. J Sex Marital Ther. 1988; 14: 184-201.

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EDITORIAL COMMENT

Penile prosthesis implantation is still the gold standard for treatment of severe erectile dysfunction (ED) when conservative treatment has failed. This intriguing surgical technique has gained a significant role in the armamentarium of treatment of ED throughout the years. The advent of new surgical tools and new infection-resistant materials has significantly reduced the risk of intra- and postoperative complications and the need for revision surgery. Nowadays implanting a penile prosthesis is the definitive solution for the treatment of organic ED, even in the era of effective and safe oral medications (1-3). Nevertheless, surgical skill and a meticulous respect for sterility rules remain fundamental requirements to guarantee the success of a penile prosthesis implant.

Paranhos et al., performed an interesting retrospective analysis on 249 patients to investigate the effectiveness of implantable penile prostheses in the treatment of ED. The results of this study demonstrated that, exchange was performed in 5.7% for fracture, inadequate size, or extrusion. A total of 24.5% of men had immediate postoperative pain, 7.9% had local infection, and 8.6% had other complications. Although, the complication rates were relatively high in the current study, nevertheless the authors adequately addressed the causes of this high figure. Infection is one of the most terrifying complications, having an incidence of 8 to 20%, as reported in large series of implants (1-3). Infections can occur a few months after surgery and a typical sign is persistent,

unchanging, or even increasing pain. The pain could be exacerbated by activating the device.

Retrospective study has its own drawback, patients were not able to remember and answer accurately about the postoperative course and complications especially after long time. Postoperatively in the current study, only 64% of the patients reported that they have sex as they had before diagnosis of ED. This is really less than the efficacy and satisfactory results that reported postoperatively in most of the literature. The majority of complications can be prevented by a proper preoperative assessment. The patient's real needs and expectations, as well as those of his partner should be addressed. The preoperative counseling should include a meticulous explanation of how the device functions and the expected complications as well as the changes that could happen in the couple's sexual life.

REFERENCES

1. Sadeghi-Nejad H: Penile prosthesis surgery: a review of prosthetic devices and associated complications. J Sex Med. 2007; 4: 296-309. Erratum in: J Sex Med. 2007; 4: 1520.
2. Natali A, Olianas R, Fisch M: Penile implantation in Europe: successes and complications with 253 implants in Italy and Germany. J Sex Med. 2008; 5: 1503-12.
3. Minervini A, Ralph DJ, Pryor JP: Outcome of penile prosthesis implantation for treating erectile dysfunction: experience with 504 procedures. BJU Int. 2006; 97: 129-33.

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Retroperitoneal LESS Donor Nephrectomy

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ABSTRACT

Donor nephrectomy with laparo-endoscopic single site (LESS) surgery has been reported via the transperitoneal approach. We describe a novel technique of retroperitoneal donor nephrectomy using a single surgical incision in the groin, below the abdominal skin crease or "bikini line". The LESS groin incision offers superior cosmesis, while the retroperitoneal approach has distinct advantages, such as the ability to identify the renal vessels early. The new procedure has been performed in two obese patients (body mass index 32 and 33 kg/m^2, respectively). The operative times were 4 and 5 hours, warm ischemic times 135 and 315 seconds, blood loss 100 and 250 mL, and hospitalization 3 and 2 days, respectively. Retroperitoneal LESS donor nephrectomy through a single, inconspicuous groin incision is feasible and safe. Further evaluation of the technique in a larger patient cohort is indicated.

Key words: *laparoscopy; nephrectomy; transplant; LESS*
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INTRODUCTION

The first laparoscopic live donor nephrectomy was reported by Ratner et al. in 1995 and retroperitoneal endoscopic donor nephrectomy was described by Yang et al. in the same year (1,2).

Laparo-endoscopic single site (LESS) donor nephrectomy is in its infancy and the optimal technique has yet to be established. The addition of needle ports or 3-5 mm ports (hybrid LESS) may make surgery easier, but may also defeat the purpose of improved cosmesis and less postoperative pain. Multichannel ports and novel bent instruments are available to overcome the lack of triangulation in single port surgery.

The complexity of the LESS approach should not be underestimated: Rajan and Turna reviewed LESS urological surgery worldwide and concluded "scissoring" may be problematic and the technique still needs to be fully evaluated with regards to benefits over standard laparoscopic approaches (3). The difficulty as well as feasibility of these procedures are underlined by Desai et al. reporting one hundred LESS cases where one patient died postoperatively as a consequence of LESS surgery (4).

In transumbilical LESS donor nephrectomy (reported initially as e-NOTES) the incision is extended up to 3 cm on either side of the umbilicus (5). This is done just prior to extraction of the kidney after the renal vessels have been transected. The cosmetic result of a scar around the umbilicus may not be acceptable to all donors, especially young females. Moreover, not using the full length of the final extraction incision during the procedure itself defies

a basic principle of surgery. Using the full length of the incision during retroperitoneal LESS surgery may allow for normal triangulation, an easier operation and a shorter learning curve.

One of the main advantages of retroperitoneal renal surgery is the ease of dissecting the renal hilum, even in obese donors. Combining the retroperitoneal route with LESS surgery as performed transperitoneally may be a significant advance in the search for the perfect donor operation. The authors have combined experience of more than 250 cases of retroperitoneal donor nephrectomy and felt it safe to proceed to single site surgery for this operation. One should be careful that this technique is only to be used by experienced retroperitoneoscopic surgeons for donor operations. As the instruments for these cases were available to us for a limited period we performed the next two cases on our donor list. No other cases have been attempted and we are in the process to further fully evaluate the technique prospectively.

SURGICAL TECHNIQUE

For right-sided donor nephrectomy, the patient is positioned in the left lateral position over a fully flexed operating table. The right hip is in mild extension to allow access to the single groin port. The patient is secured with strapping to the table, to allow maneuverability of the table during surgery. Instruments for laparoscopic as well as open surgery are kept at hand in case emergency conversion to open surgery is required (Table-1).

An incision 6 cm long is made in the groin, below the "bikini line". The incision is deepened with open surgical technique (muscle splitting) to enter the retroperitoneal space. The psoas muscle is identified and the space posterior to the kidney is developed as described by Bachmann et al. (6). An inflation balloon (PDB 1000 Covidien, Mansfield, MA) is deployed behind the kidney and inflated with 800 mL air (Figure-1).

The Gelport™ (Applied Medical, Rancho Santa Margarita, CA) is placed in the incision and carbon dioxide pressure is established at 12 mm Hg via the central 10 mm camera port (Figure-2). Surgical adhesive film is centrally placed over the Gelport™ to control gas leak. Two 5 mm ports are placed on either side of the lens on the edges of the Gelport™.

Gerota's fascia is opened close to the psoas muscle to expose the fatty tissue harboring the inferior vena cava and renal vessels. The vena cava is followed cranially to the renal vein. The renal artery pulsation is identified to the left of this in the fatty tissue and dissected free. A 5.5 mm 30° lens is used for the hilar dissection, so clashing between instruments is reduced. A curved fenestrated grasper is inserted via the Gelport™ inferior rim and is used to grasp the edge of Gerota's fascia to keep fat from obscuring the view.

The hilar vessels are dissected free to allow enough space for a vascular stapler to pass without

Table 1 *– Instruments used for retroperitoneal LESS donor nephrectomy.*

Instrument	Use
Gelport™ -	Placed in groin incision to allow triangulation
Bariatric bipolar grasper (Karl Storz™)	Needed for dissection on cranial part of hilum
Bariatric scissors (Karl Storz™)	As above and to mobilise the upper pole
Curved LESS grasper (Karl Storz™)	Portless via Gelport™ to retract fat
Lens 10 mm 30° normal length (Karl Storz™)	Initial part of operation
Lens 5.5 mm 30° bariatric length (Karl Storz™)	Hilar dissection and vessel stapling
Lens 10 mm 45° bariatric length (Karl Storz™)	Adrenal and upper pole dissection
Large endo-bag (Covidien™)	To hold kidney up to expose pedicle for stapler
TA 30 vascular stapler (Covidien™)	To occlude and cut renal artery and vein

Figure 1 *– An inflation balloon is inserted retroperitoneally via the 6 cm groin incision below the "bikini line".*

catching tissue behind the vessels in the stapler jaws. The adrenal is dissected from the kidney using the 10 mm 45° lens. The adrenal artery is clipped close to the renal artery to prevent it from hanging in the potential staple line. The ureteric dissection is completed, preserving maximal tissue around the ureter, which is clipped and cut distally.

The kidney is freed from the peri-renal fat using the 45° lens for the upper pole and using the curved grasper to allow counter-traction on the perirenal fat. Once the kidney is completely free the renal vessels are inspected for safety prior to stapling. The 5.5 mm 30° bariatric lens is used and rotated 180° to visualize the hilum maximally and reduce clashing due to the small diameter of the lens.

Figure 2 *– The Gelport™ in use. Note that the surgeon stands on the abdominal side of the patient, which is unusual for retroperitoneal surgery.*

A 15 mm large laparoscopic retrieval bag (EndoCatch II, Covidien, Mansfield, MA) is inserted via the right side of the Gelport™ (without the use of an extra port), deployed over the kidney and closed partially to expose the hilum. Great care is taken to protect the vessels from the plastic covered metal rim of the bag as described elsewhere (7).

A 5-12 mm port (Applied Medical, Rancho Santa Margarita, California) is placed on the left side of the Gelport to allow a vascular stapler as well as the laparoscopic scissors easy and rapid exchange. The kidney is elevated with the retrieval bag (with the ureter visible and free) and the renal artery is stapled (TA 30 linear stapler - Covidien, Mansfield, MA) and cut with laparoscopic scissors. The renal vein is managed in similar fashion. The kidney is removed together with the outer covering of the Gelport™ and processed immediately in slushed ice and Euro-Collins solution. Furosemide and mannitol are not routinely administered intravenously prior to harvesting.

The procedure has been performed on two obese male donors (BMI 32 kg/m^2 and 33 kg/m^2, respectively). Routine extensive workup was done and informed consent was obtained. In both cases the right kidney was harvested, as it appeared more suitable on preoperative CT angiography. The patients were placed under general anesthesia with mechanical ventilation and full muscle relaxation to enlarge the retroperitoneal working space maximally.

Surgical time was 4 hours and 5 hours, respectively. Warm ischemic times (measured from the time of renal artery occlusion until fluid is seen exiting from the renal vein during perfusion with cold Euro-Collins solution) were 135 seconds and 315 seconds, respectively (the latter time was prolonged due to dislodgement of the camera port from the Gelport™). Blood loss was 100 mL and 250 mL (calculated and recorded by the attending anesthetist). Hospital stay was 3 and 2 days, respectively. Both patients were pain-free on discharge. The postoperative result after removal of the wound drain is shown in Figure-3. Both kidneys functioned well postoperatively.

Figure 3 *– Groin incision at discharge of patient on postoperative day 3.*

COMMENTS

A recent report described live donor nephrectomy using pure LESS surgery via a high Pfannenstiel incision and transperitoneal route (8). The authors elevated a flap of skin to allow triangulation and exchanged ports for dissection and stapling. While this is an ingenious novel approach, the angle from the midline lower abdominal incision to the upper pole and hilum of the kidney may be difficult, especially in more obese patients. The same team reported a matched comparison (retrospectively) between standard laparoscopy and their Pfannenstiel LESS approach. No difference in postoperative pain, hospital stay or analgesic requirements were found between the two groups. This suggested cosmesis may be the only difference (9). However, we believe the elevation of flaps (in contrast to our retroperitoneal LESS approach) may contribute to increased pain postoperatively.

The Gelport™ used in the new technique described above allows for multiple atraumatic port exchanges and reduces warm ischemic time, as the opening in the abdominal wall is created at the start of surgery. It utilizes the full length of the incision during surgery and can be seen as an advance, compared to the use of a multi-port device with lack of triangulation, and extension of the incision at the time of graft extraction as described by Gill et al. (5).

A novel approach quite similar to ours were used by Rye et al. where they used the base of the Gelport™, the Alexis™ ring, to affix a surgical glove and use the fingers as port sites in 14 successful urological procedures (10).

Fatal complications related to living donor nephrectomy are associated with both locking- and non-locking surgical clips (11). The potential safety of LESS is probably comparable to open surgery and ordinary laparoscopic surgery, and is primarily related to the technique used for occlusion of the renal vessels.

In the technique described by Gill et al. (5) the donor kidney is pulled up against the abdominal wall while the skin incision is enlarged to allow removal of the kidney. The pressure on the kidney and the prolonged warm ischemic time may be detrimental to renal function. The Gelport™ LESS technique described above has the advantage that no further incisions are made after the initial dissection.

Canes et al. performed a matched-pair comparison of LESS versus standard laparoscopic left donor nephrectomy and found significantly longer warm ischemic times in the LESS group (12). This is probably related to additional time required for extension of the incision after the renal vessels have been severed and the donor kidney is being extracted.

The superior cosmetic result achieved by retroperitoneal LESS surgery may contribute significantly to the recruitment of more kidney donors. The in-hospital pain scores are similar after LESS compared with laparoscopic live donor nephrectomy, but when out-of-hospital pain scores are reviewed, LESS donors report significantly less pain and quicker return to 100% function (12).

CONFLICT OF INTEREST

Karl Storz supplied the instruments and Surgical Innovations SA the Gelports™ and ports.

REFERENCES

1. Ratner LE, Ciseck LJ, Moore RG, Cigarroa FG, Kaufman HS, Kavoussi LR: Laparoscopic live donor nephrectomy. Transplantation. 1995; 60: 1047-9.

2. Yang SC, Park DS, Lee DH, Lee JM, Park K: Retroperitoneal endoscopic live donor nephrectomy: report of 3 cases. J Urol. 1995; 153: 1884-6.
3. Rajan P, Turna B: New trends in minimally invasive urological surgery. Int Braz J Urol. 2009; 35: 514-20.
4. Desai MM, Berger AK, Brandina R, Aron M, Irwin BH, Canes D, et al.: Laparoendoscopic single-site surgery: initial hundred patients. Urology. 2009; 74: 805-12.
5. Gill IS, Canes D, Aron M, Haber GP, Goldfarb DA, Flechner S, et al.: Single port transumbilical (E-NOTES) donor nephrectomy. J Urol. 2008; 180: 637-41; discussion 641.
6. Bachmann A, Dickenmann M, Gürke L, Giannini O, Langer I, Gasser TC, et al.: Retroperitoneoscopic living donor nephrectomy: a retrospective comparison to the open approach. Transplantation. 2004; 78: 168-71.
7. Bollens R, Mikhaski D, Espinoza BP, Rosenblatt A, Hoang AD, Abramowicz D, et al.: Laparoscopic live donor right nephrectomy: a new technique to maximize the length of the renal vein using a modified Endo GIA stapler. Eur Urol. 2007; 51: 1326-31.
8. Andonian S, Herati AS, Atalla MA, Rais-Bahrami S, Richstone L, Kavoussi LR: Laparoendoscopic single-site pfannenstiel donor nephrectomy. Urology. 2010; 75: 9-12.
9. Andonian S, Rais-Bahrami S, Atalla MA, Herati AS, Richstone L, Kavoussi LR: Laparoendoscopic single-site pfannenstiel versus standard laparoscopic donor nephrectomy. J Endourol. 2010; 24: 429-32.
10. Ryu DS, Park WJ, Oh TH: Retroperitoneal laparoendoscopic single-site surgery in urology: initial experience. J Endourol. 2009; 23: 1857-62.
11. Friedman AL, Peters TG, Jones KW, Boulware LE, Ratner LE: Fatal and nonfatal hemorrhagic complications of living kidney donation. Ann Surg. 2006; 243: 126-30.
12. Canes D, Berger A, Aron M, Brandina R, Goldfarb DA, Shoskes D, et al.: Laparo-endoscopic single site (LESS) versus standard laparoscopic left donor nephrectomy: matched-pair comparison. Eur Urol. 2010; 57: 95-101.

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EDITORIAL COMMENT

Since its original description in 1991, urologic laparoscopy has shown exponential growth (1). The laparoscopic technique has been associated with reduced postoperative pain, improved cosmesis, decreased hospital stay, and improved convalescence while maintaining equivalent outcomes to open surgery. As innovations have been incorporated, a natural progression has led to the evaluation of the number of ports required to safely perform laparoscopic procedures. This interest has intensified with the realization that a decrease in port size and number of ports could decrease operative morbidity leading to reduced narcotic requirements, bleeding risk, shorter hospital stay, a faster return to work, and improved cosmetic outcome (2).

While making the transition from conventional laparoscopy to Laparoendoscopic single-site (LESS) procedures, many technical challenges have been encountered (3). Inherent to the use of a common abdominal entry point is instrument crowding. This crowding leads to a loss of triangulation and tissue manipulation, mainstays in conventional laparoscopy, thus significantly increasing the technical difficulty of LESS procedures. Similarly, crowding leads to internal and external clashing of instruments and handles which is often noted as the most frustrating aspect of LESS.

The authors used the GelPort™ as the access platform, which can help to provide adequate spacing, triangulation and flexibility of port placement for LESS procedures. Another advantage is that the opening in the abdominal wall created at the start of surgery for device placement is also used for graft extraction.

The authors should be congratulated for their elegant work using alternative ways for donor nephrectomies. Andonian et al. (4) had already compared LESS Pfannenstiel donor nephrectomy with a contemporary series of standard laparoscopic donor nephrectomies, with no significant difference in terms of operative time, warm ischemia time (WIT), estimated blood loss, median length of stay and narcotic requirements. The Retroperitoneal LESS technique described by the authors has the advantages of retroperitoneal approach and better aesthetic appearance.

In our initial experience with LESS we performed an extraperitoneal radical nephroureterectomy through a 5 cm Gibson incision with Gelport and conventional instruments. Working space was obtained with open medial mobilization of the colon and the kidney before the location of Alexis' retractor. The surgeon's view in this procedure is inferior and distal to the renal pedicle. Pelvic ureter was dissected by the incision to improve the localization of anatomical landmarks after installation of pneumoretroperitoneum. Renal vessels could be controlled en bloc with an endoscopic stapler. Superior pole dissection was facilitated by distal traction of ureter. The kidney was removed through the incision and the bladder cuff was completed utilizing open technique and the same incision.

In donor nephrectomy, further caution must observed concerning WIT. In this present paper a higher operative and WIT compared to standard laparoscopy and LESS Pfannenstiel donor nephrectomy were reported. This can be adverse for the graft and for the donor. Although improved cosmesis is important, all efforts should be made to keep surgery as safe as possible either for donor or for recipient.

In our opinion, this novel technique should only be attempted by experienced laparoscopic surgeons who are comfortable in performing standard retroperitoneal laparoscopic donor nephrectomies.

LESS certainly represents the next step forward in the arena of minimally invasive surgery. However, for patients who undergo donor nephrectomy larger prospective randomized trials are needed to compare the postoperative pain levels, WIT, blood loss, operative time and graft function before it gains widespread acceptance.

REFERENCES

1. Clayman RV, Kavoussi LR, Soper NJ, Dierks SM, Merety KS, Darcy MD, Long SR, Roemer FD, Pingleton ED, Thomson PG: Laparoscopic nephrectomy. N Engl J Med. 1991; 324: 1370-1.
2. Raman JD, Bagrodia A, Cadeddu JA: Single-incision, umbilical laparoscopic versus conventional laparoscopic nephrectomy: a comparison of perioperative

outcomes and short-term measures of convalescence. Eur Urol. 2009; 55: 1198-204.
3. Canes D, Desai MM, Aron M, Haber GP, Goel RK, Stein RJ, Kaouk JH, Gill IS: Transumbilical single-port surgery: evolution and current status. Eur Urol. 2008; 54: 1020-9.
4. Andonian S, Rais-Bahrami S, Atalla MA, Herati AS, Richstone L, Kavoussi LR: Laparoendoscopic single-site Pfannenstiel versus standard laparoscopic donor nephrectomy. J Endourol. 2010; 24: 429-32.

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EDITORIAL COMMENT

In this manuscript, the authors propose a novel LESS approach using a surgical incision in the groin and report their experience with 2 obese patients. The authors are to be congratulated for exploring alternative ways for donor nephrectomies. Our group has recently described an alternative surgical technique that relies on the classic laparoscopic approach, supported by insertion of the surgeon's hand during kidney recovery using a lateral paramedian incision (1). We prefer a hand-assisted technique, because this approach is particularly useful when an incision is necessary to remove an intact surgical specimen in a short time after vessel division.

The LESS technique combines the advantages of retroperitoneal approach with the improved cosmesis and decreased discomfort. This experience represents a further effort to show that single port surgery is feasible and reproducible technique even in particular procedure such as living donor nephrectomy. Other Authors using NOTES technique are developing an incision-free procedure with graft delivery through a transvaginal incision in female donors with excellent aesthetic results (2).

However, the authors should proceed with caution when describing novel technique for renal recovery. While they have a wide experience with retroperitoneal donor nephrectomies, it should be emphasized that the approach described has to be attempted only by experienced laparoscopic surgeons who are comfortable in standard retroperitoneoscopic nephrectomies.

The rush for the development of new procedures carries the pitfall to publish papers with a low number of cases that may not represent the surgical reality. Moreover, taking in the account the difficulty and the risks of the procedure, the greater question that remains to be answered concerns the proper place of the LESS and NOTES approaches in urologic surgery. It is clear we can do this but far less clear that we should (3).

REFERENCES

1. Selvaggi FP, Ditonno P, Lucarelli G: Transperitoneal deviceless hand-assisted laparoscopic living donor nephrectomy: an alternative technique for kidney recovery. J Endourol. 2010. [Epub ahead of print]
2. Alcaraz A, Musquera M, Peri L, Transvaginal Notes-Assisted laparoscopic living donor nephrectomy. Am J Tansplant.2010; 10 (suppl. 4); A219.
3. Strup SE. Editorial Comment on: Laparoendoscopic single-site Pfannenstiel donor nephrectomy. J Urol. 2010; 183: 1871; discussion 1872.

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The Position of the Testis during the Fetal Period. An Additional Parameter to Estimate Fetal Weight

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ABSTRACT

Purpose: To establish a correlation between testicular position and fetal weight, in order to provide an additional prenatal parameter for fetal weight estimation.
Materials and Methods: We studied 288 testes from 144 human fetuses. The fetuses were assessed as regards weight, total length, crown-rump length and foot length. Fetal age was calculated according to the foot length criteria. The position of the testis was classified as abdominal, inguinal or scrotal.
Results: One hundred and ninety seven testes (68.4%) were abdominal, 43 (14.9%) were inguinal and 48 (16.6%) were scrotal. In the fetuses weighing up to 500 grams, 147 testes (93.5%) were abdominal and 5 testes (6.5%) were inguinal. In fetuses weighing between 501 and 1000 grams, 54 testes (68.6%) were abdominal, 28 testes (32.5%) were inguinal and 4 testes (4.6%) were scrotal. In fetuses weighing between 1001 and 1500 grams, 4 testes (13.3%) were abdominal, 3 (10%) were inguinal and 23 (76.6%) were scrotal. All fetuses weighing more than 1500 grams presented the testes with a migration to the scrotum (10 fetuses - 20 testes).
Conclusions: To our knowledge, this is the first study correlating the testicular position to the fetal weight during testicular migration in human fetuses. Identification of the testes during the prenatal period could be a useful alternative parameter for estimating fetal weight.

Key words: testis; migration; fetal development; fetal weight; prenatal ultrasound; prematurity
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INTRODUCTION

The human testis develops in the abdomen and migrates to the scrotum during the second trimester of gestation, completing the process near the 30th week after conception (1). Testicular migration is divided into two phases; the first phase corresponds to the migration of the testis from the abdomen to the internal inguinal ring, whereas the second phase corresponds to the passage of the testis through the inguinal canal, until its final destination in the scrotum (2).

The main theories that attempt to explain the testicular migration process are the increase of intra-abdominal pressure (3), the development of testicular gubernaculum, the development of the processus vaginalis, inguinal canal and spermatic vessels (2) as well as the production of gonadotrophins by the placenta that stimulates the production of testicular androgens (4).

Certain parameters can be used to estimate the fetal weight by ultrasound, as abdominal circumference, femur length, and size of the fetal head (5). Although they are not precise, these parameters are

still used in routine practice, especially to detect low and very low birth weights (less than 1500 g). Low birth weight infants can present various complications after conception, thereby influencing the growth and health of the individual in the future (6).

The aim of this study was to establish a correlation between the position of the testis and fetal weight, in order to use the testicular position as an additional prenatal ultrasonic parameter for fetal weight estimation.

MATERIALS AND METHODS

We studied 288 testes from 144 fresh human male fetuses that died of causes unrelated to the urogenital tract. The fetuses were macroscopically well preserved and no external evidence of congenital malformation was detected. After death, the fetuses were maintained refrigerated (4º C) for a period of 24 to 72 hours. Then, the fetuses were analyzed based on their morphometric parameters (weight, total length, crown-rump length and foot length). All measurements were performed by the same investigator. The gestational age of the fetuses was determined in weeks post conception, according to the foot length criteria, which currently is the most acceptable method to estimate the fetal age (7-10).

The abdominal and pelvic cavities were opened, and the position of the testes was determined. The testis was regarded as abdominal when it was proximal to the internal inguinal ring, canalicular or inguinal when it was between the internal and external inguinal ring, and descended or scrotal when it was inferior to the external ring (1).

The present study was approved by the State University of Rio de Janeiro Bioethics Committee and all parents signed an informed consent form

RESULTS

Of the 288 testes studied, 197 (68.4%) were abdominal, 43 (14.9%) were inguinal and 48 (16.6%) were scrotal.

The relationships between fetal weight and the position of the testis are shown in Figure-1.

In fetuses weighing up to 500 grams (76 fetus - 152 testes), 147 testes (93.5%) were abdominal and 5 (6.5%) were inguinal.

In fetuses weighing between 501 and 1000 grams (43 fetuses - 86 testes), 54 testes (68.6%) were abdominal, 28 (32.5%) were inguinal and only 4 (4.6%) had completed their migration (scrotal). All 4 testes that had migrated to the scrotum were in fetuses weighing more than 970 grams. No testis in the scrotum was found in any fetuses weighing less than 970 grams.

In fetuses weighing between 1001 and 1500 grams (15 fetuses - 30 testes), 4 testes (13.3%) were abdominal, 3 (10%) were inguinal and 23 (76.6%) were scrotal. All fetuses weighing more than 1500 grams presented the testes in the scrotum (10 fetuses - 20 testes).

Comments

Various parameters have been proposed to determine the gestational age of human fetuses, such as crown-rump length, femur length, fetal weight, biparietal diameter, orbital and frontal bone diameter and foot length (7-9. 11-13). After the 12th gestational week, in the event that the last menstruation date was not known, the foot length measurement is considered by ultrasonographists, morphologists, obstetricians and perinatologists as being the best parameter to determine the gestational age (7-9).

Studies that correlate the position of the testes and the gestational age in human fetuses are scarce (1,14). Sampaio and Favorito (1) have previously reported the chronology of testicular migration in human fetuses in a sample of 73 fetuses (146 testes). However, only limited importance has been given to the correlation between the fetal weight and the position of the testes during the fetal period. To our knowledge, there are no reported studies correlating the fetal weight to the position of the testes analyzing a significant number of human fetuses.

The estimate of fetal weight during ultrasound screening is of practical importance, especially in pregnant women who are clinically suspected of delivering low and very low birth weight infants (less than 1500 grams) (15). The identification of possible

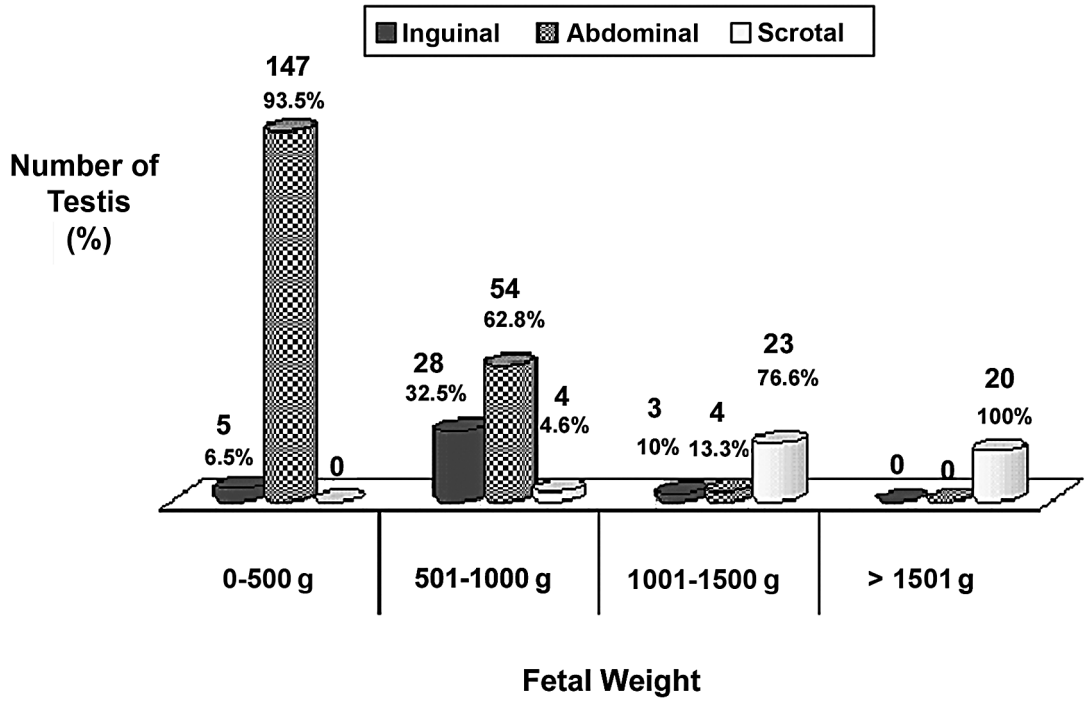

Figure 1 *– Relationships between the position of the testes and the fetal weight during the fetal period in 288 testes studied.*

low birth weight infants before their conception would permit early stage monitoring. Low birth weight infants can present major complications during and after delivery. In fact, it has previously been demonstrated that pregnant women who presented this possibility at prenatal examination and strictly monitored had a lower rate of fetal complications (16).

The most frequently used parameters in obstetric ultrasound to calculate fetal weight is not considered highly accurate (17). Recently, the use of the formula (fetal weight = 5381.193 + 150.324 x head circumference + 2.069 x femur length + 0.0232 x abdominal circumference x 3-6235.478 x logarithm of the head circumference) was developed. This formula incorporates the most frequently used fetal biometric parameters for ultrasound measurements that have proved to be easier and more accurate in estimating the weight of fetuses weighing less than 1600 grams (18).

The visualization of the fetal testis is feasible by intrauterine ultrasound during gestation, also making possible the measurement of testicular diameters and their position in the abdomen, pelvis or scrotum (19-21).

In the present study, we found that in fetuses weighing less than 970 grams no testes had completed the migration to the scrotal position. Thus, when the testis cannot be visualized in the scrotum, this should indicate that the fetus would probably weigh less than 1000 grams.

When analyzing fetuses weighing between 1001 and 1500 grams, only 13% of the testes were positioned in the abdomen and more than 76% of the testes had already completed their migration to the scrotum. All fetuses weighing more than 1500 grams had their testes positioned in the scrotum. We did not find any fetus weighing less than 970 grams that had completed testicular migration.

If the testes are still in the abdomen during a prenatal ultrasonic assessment, this fetus has a 70% of chance of weighing less than 1000 grams and a 13% chance of weighing between 1000 and 1500 grams. If the testes are in the scrotum, the fetus has an approximately 5% chance of weighing less than 1000 grams and a 75% chance of weighing between 1000 and 1500 grams. The evaluation of testicular position ultrasound evaluation would be a viable and useful alternative for estimating the fetal weight.

CONFLICT OF INTEREST

None declared.

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REFERENCES

1. Sampaio FJ, Favorito LA: Analysis of testicular migration during the fetal period in humans. J Urol. 1998; 159: 540-2.
2. Heyns CF, Hutson JM: Historical review of theories on testicular descent. J Urol. 1995; 153: 754-67.
3. Frey HL, Rajfer J: Role of the gubernaculum and intraabdominal pressure in the process of testicular descent. J Urol. 1984; 131: 574-9.
4. Husmann DA, Levy JB: Current concepts in the pathophysiology of testicular undescent. Urology. 1995; 46: 267-76.
5. Mladenovic-Segedi L, Segedi D: Accuracy of ultrasonic fetal weight estimation using head and abdominal circumference and femur length. Med Pregl. 2005; 58: 548-52.
6. Hack M, Schluchter M, Cartar L, Rahman M, Cuttler L, Borawski E: Growth of very low birth weight infants to age 20 years. Pediatrics. 2003; 112: e30-8.
7. Hern WM: Correlation of fetal age and measurements between 10 and 26 weeks of gestation. Obstet Gynecol. 1984; 63: 26-32.
8. Mercer BM, Sklar S, Shariatmadar A, Gillieson, MS, D'Alton MK: Fetal foot length as a predictor of gestacional age. Am J Obst Gynecol. 1987; 156: 350-6.
9. Platt LD, Medearis AL, DeVore GR, Horenstein JM, Carlson DE, Brar HS: Fetal foot length: relationship to menstrual age and fetal measurements in the second trimester. Obstet Gynecol. 1988; 71: 526-31.
10. Favorito LA, Albuquerque LF, Sampaio FJ, Costa WS: Disposition of the striated sphincter and its relation to the prostate in human fetuses. Int Braz J Urol. 2007; 33: 414-20.
11. Mantoni M, Pedersen JF: Fetal growth delay in threatened abortion: an ultrasound study. Br J Obstet Gynaecol. 1982; 89: 525-7.
12. Warda AH, Deter RL, Rossavik IK, Carpenter RJ, Hadlock FP: Fetal femur length: a critical reevaluation of the relationship to menstrual age. Obstet Gynecol. 1985; 66: 69-75.
13. Kopta MM, May RR, Crane JP: A comparison of the reliability of the estimated date of confinement predicted by crown-rump length and biparietal diameter. Am J Obstet Gynecol. 1983; 145: 562-5.
14. Achiron R, Pinhas-Hamiel O, Zalel Y, Rotstein Z, Lipitz S: Development of fetal male gender: prenatal sonographic measurement of the scrotum and evaluation of testicular descent. Ultrasound Obstet Gynecol. 1998; 11: 242-5.
15. Cicognani A, Alessandroni R, Pasini A, Pirazzoli P, Cassio A, Barbieri E, et al.: Low birth weight for gestational age and subsequent male gonadal function. J Pediatr. 2002; 141: 376-9.
16. Lindqvist PG, Molin J: Does antenatal identification of small-for-gestational age fetuses significantly improve their outcome? Ultrasound Obstet Gynecol. 2005; 25: 258-64.
17. Ben-Haroush A, Yogev Y, Hod M, Bar J: Predictive value of a single early fetal weight estimate in normal pregnancies. Eur J Obstet Gynecol Reprod Biol. 2007; 130: 187-92.
18. Schild RL, Fell K, Fimmers R, Gembruch U, Hansmann M: A new formula for calculating weight in the fetus of < or = 1600 g. Ultrasound Obstet Gynecol. 2004; 24: 775-80.
19. Rotondi M, Valenzano F, Bilancioni E, Spano G, Rotondi M, Giorlandino C: Prenatal measurement of testicular diameter by ultrasound: development of fetal male gender and evaluation of testicular descent. Prenat Diagn. 2001; 21: 112-5.
20. Pinette MG, Wax JR, Blackstone J, Cartin A: Normal growth and development of fetal external genitalia

demonstrated by sonography. J Clin Ultrasound. 2003; 31: 465-72.
21. Mazza V, Di Monte I, Pati M, Contu G, Ottolenghi C, Forabosco A, Volpe A. 2004. Sonographic biometrical range of external genitalia differentiation in the first trimester of pregnancy: analysis of 2593 cases. Prenat Diagn 24: 677-684.

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Efficacy of Transcutaneous Functional Electrical Stimulation on Urinary Incontinence in Myelomeningocele: Results of a Pilot Study

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ABSTRACT

Purpose: To investigate the efficacy of transcutaneous functional electrical stimulation (FES) on voiding symptoms in children with myelomeningocele (MMC) suffering from neuropathic urinary incontinence.
Materials and Methods: Six girls and 6 boys with moderate to severe urinary incontinence secondary to MMC were included. Median age of children was 5.04 (range: 3-11) years. They underwent a urodynamic study (UDS) before and 3 months after FES with special attention to detrusor leak point pressure (DLPP) and maximal bladder capacity (MBC). Daily incontinence score, frequency of pad changing, and enuresis were also assessed before and three months after treatment. Fifteen courses of FES for 15 minutes 3 times per week were performed with low frequency (40 Hz) electrical current, duration of 250μs, with hold and rest time of 2 seconds.
Results: Nine children had improvement on urinary incontinence score, while three children had no improvement. Median DLPP was significantly increased from 38.5 (range: 12-50) cm H_2O to 59.5 (range: 18-83) cm H_2O (P = 0.003). MBC was significantly increased from median value of 155 (range: 60-250) mL to 200 (range: 110-300) mL (P = 0.007).
Conclusions: This is a pilot study showing that FES therapy might have positive effects on improvement of voiding symptoms of MMC children with neurogenic urinary incontinence in terms of daily incontinence score and UDS parameters.

Key words: *myelomeningocele; functional electrical stimulation; urinary incontinence*
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INTRODUCTION

Myelomeningocele (MMC) is the most common cause of neurogenic bladder in children. Bladder function in these children is affected by disordered innervation of detrusor muscle and external urethral sphincter that may lead to hydronephrosis or reflux and finally renal failure with life-threatening consequences (1). Treatment of urinary system dysfunction is primarily aimed at preventing upper urinary tract damage and secondarily at gaining continence and improving quality of life and social interactions (2). Initial treatment is based on clean intermittent catheterization (CIC) and anticholinergic medications. In those who fail to respond to medical treatment, surgical procedures might be needed (3).

Electrical stimulation has been used for the treatment of urinary incontinence in adults for several decades and recently in children (4,5).

Most authors believe that nonimplanted electrical stimulation induces action potential in the afferent fibers of pudendal nerve leading to efferent outflow causing contraction of the striated pelvic floor musculature. In addition, inappropriate

detrusor activity might be inhibited by this modality (6).

Functional electrical stimulation (FES) is the application of electrical current to the excitable tissue to improve function that is lost in neurologically impaired individuals. It is a useful noninvasive therapeutic option that is used as a conservative treatment with positive results in bladder overactivity (7).

Many patients with urge, stress and mixed urinary incontinence have been treated with FES using anal or vaginal electrodes which resulted in inhibitory reflexes against spontaneous detrusor contraction (8).

To our knowledge, there has been no reported study evaluating the effects of transcutaneous functional electrical stimulation on urinary incontinence and urodynamic study (UDS) parameters in MMC children. This therapeutic option was used in form of a pilot study to improve urinary incontinence symptoms in MMC patients.

MATERIALS AND METHODS

Between August 2007 and March 2009, 12 children (6 boys and 6 girls) with neuropathic urinary incontinence secondary to MMC who were referred to our clinic at Children's Hospital Medical Center, Tehran University of Medical Sciences, were enrolled in the present study. This study was approved by the local Ethics Committee and written informed consent was obtained from all children's caregivers. Inclusion criteria were defined as children with MMC, aged more than 3 years and moderate to severe urinary incontinence with unsatisfactory response to conventional treatment (requiring CIC every 3 to 4 hours and use of pads). Urological evaluation consisted of renal ultrasonography, urinalysis and UDS. Urodynamic parameters including mean bladder capacity (MBC) and detrusor leak point pressure (DLPP), were recorded according to recommendations by International Children's Continence Society (ICCS) (9).

Daily incontinence score, the episodes of nighttime wetting (the number of nights that the child involuntarily micturates during sleep in a one-week period) and frequency of pad changing (the number of leakage episodes between two consecutive CICs) were recorded in a voiding diary by parents. The daily incontinence score was recorded on a 0-3 scale, as described by Schurch et al. score 0, completely dry; 1, wet once a day, usually at night (mild); 2, wet for < 50% of the time between CIC (moderate); and 3, wet for > 50% of the time between CIC (severe) (10). A decrement of 2 or more degrees in the daytime incontinence score was considered as "improvement".

UDS (F.M. Wiest Medizintechnik GmbH, Unterhaching, Germany) was performed according to recommendations by the ICCS in all patients in a supine position (9). The intravesical and abdominal pressures were measured simultaneously with a double lumen catheter and with a rectal balloon catheter. EMG was recorded with superficial electrodes in the perineal area. Special attention was given to detrusor leak point pressure (DLPP) and maximal bladder capacity. The same protocol was used for the UDS performed three months after FES courses. Anticholinergic medications were discontinued at least seven days prior to both UDS sessions. Subjective success was assessed by voiding diary and was compared to objective measurements of UDS.

Following the pretreatment UDS, conventional treatment (anticholinergic and CIC) was continued and children received 15 courses of transcutaneous FES for 15 minutes in each session, 3 times per week.

The same electrical stimulation device (model 755X, one-channel NOVIN, Isfahan, Iran) was used for all the patients. Stimulation was delivered with an adjustable power setting. Two rectangular self-adhesive (2.5 × 2.5 cm) electrodes were used. Positive electrode was placed on the skin above the pubic symphysis, and the negative one was placed on the skin under urethra.

In all treatment sessions, we used 40 Hz frequency (to cover both the irritative and obstructive symptoms and stimulate striated muscle fibers and urethral sphincter in pelvic floor), duration of 250μs with hold and rest time of 2 seconds. The intensity was increased until the child experienced a strong but comfortable level of muscle contractions. Maximum current intensity was below the pain threshold and well tolerated by the children. In younger children, an intensity setting of < 30 mA was used. Median current intensity in others was 40 (range: 20-65) mA.

Children were followed for more than 3 months. All patients underwent UDS three months after the 15 courses of FES.

Statistical analysis was performed by SPSS 16.0 software (SPSS Inc., Chicago, IL). The Wilcoxon-Signed rank test was executed for non parametric statistical comparisons before and after treatment. P value of less than 0.05 was considered statistically significant.

RESULTS

Twelve MMC children including six girls and six boys were enrolled in the present study. Median age of the patients was 5.04 (range: 3-11 years). Demographic data of children are described in Table-1.

Two of twelve patients became completely dry between two consecutive CICs. Daily incontinence score was improved from 3 to 1 in five children. Three children remained unchanged for their daily incontinence score. Of those three children who failed to respond to electrical stimulation, two were totally incontinent (Daily incontinence score: 3) initially before the treatment.

Details of voiding characteristics and UDS parameters before and after FES therapy are summarized in Table-2. Overall, median daily incontinence score was improved from 3 (range: 2-3) to 1 (range: 0-3) (P = 0.006). Median frequency of pad changing was significantly decreased from 6 (range: 2-8) to 2 (range: 0-7) times/day (P = 0.004). Median episodes of night wetting was 3 (range: 2-7) night/week before the electrical stimulation, which improved to 2 (range: 1-7) night/week after the treatment (P = 0.06).

Both of two UDS parameters were significantly improved after treatment. Median DLPP was significantly increased from 38.5 (range: 12-50) cm H_2O to 59.5 (range: 18-83)cm H_2O (P = 0.003). MBC was significantly increased from median value of 155 (range: 60-250) mL to 200 (range: 110-300) mL (P = 0.007). No significant adverse effect was reported by the children and their parents after treatment.

Table 1 – *Clinical features and underlying pathology of children with myelomeningocele.*

Patient	Age (years)	Gender	Level of MMC†	Concurrent Disability	Movement Weakness
1	5	M	Sacral	Club foot	Distal
2	4	F	Lower lumbar	Club foot	Distal
3	10	M	Sacral	None	Normal
4	4	F	Lower lumbar	Club foot DDH‡	Distal
5	4	F	Sacral	None	Normal
6	11	M	Lower lumbar	None	Distal
7	3.5	F	Upper lumbar	DDH	Paraplegic
8	3.5	M	Lower lumbar	Club foot	Distal
9	3	F	Upper lumbar	Hydrocephalus	Paraplegic
10	3	M	Lower lumbar	Club foot DDH	Distal
11	6	F	Upper lumbar	Hydrocephalus DDH	Paraplegic
12	3.5	M	Lower lumbar	Club foot	Distal

MMC = myelomeningocele; DDH = developmental dislocation of hip.

Table 2 – *Voiding and urodynamic parameters of children before and after FES therapy.*

Patient	Daily Incontinence Score		Frequency of Pad Changing (times/day)		Enuresis (night/weak)		DLPP (cm H_2O)		MBC (mL)	
	Before	After	Before	After	Before	After	Before	After	Before	After
1	3	0	7	0	3	2	40	74	250	300
2	3	1	7	2	4	4	40	60	250	260
3	3	3	7	7	7	7	44	48	160	170
4	2	0	6	2	3	1	12	18	190	200
5	2	1	2	1	2	2	16	38	180	200
6	3	2	8	5	2	2	35	48	100	200
7	3	1	4	1	3	2	35	83	150	250
8	3	2	6	2	2	2	40	59	60	130
9	2	2	5	2	7	7	50	62	130	190
10	3	1	6	3	3	1	39	60	110	110
11	3	1	5	2	3	3	38	75	200	200
12	3	3	4	4	2	2	30	30	110	110

DLPP = detrusor leak point pressure; FES = functional electrical stimulation; MBC = maximal bladder capacity.

COMMENTS

Myelomeningocele repair is still challenging in the literature. Unfavorable effects of prenatal intervention on postnatal bladder function include poor compliance, poor detrusor contractility, detrusor-sphincter dyssynergia, hydronephrosis and vesicoureteral reflux. This may highlight the existence of bladder developmental defects in these children (11).

In patients with MMC, hyperactivity or inactivity of either detrusor or external urethral sphincter leads to bladder-sphincter dysfunction and ultimately urinary incontinence and poor quality of life. In most of the children, urinary continence can be gained with bladder emptying by CIC and anticholinergic medication.

Continent catheterizable urinary diversion is applied in patients who do not respond to anticholinergic medications. However, it may be complicated by urinary tract infection, distal dehiscence of conduit, stomal stenosis, and urinary stomal leakage (12).

Mini-invasive collagen sling has also been used as a safe and easy method with promising immediate results in patients with neurogenic urinary incontinence. However, a one-year follow-up study failed to demonstrate beneficial long term outcome (13).

Electrical stimulation, as a clinical non-invasive treatment option to manage the urinary incontinence symptoms, was first introduced by Caldwell and colleagues (14).

Numerous electrical stimulation methods have been reported to be effective for the treatment of lower urinary tract dysfunction (15).

There are many evidences that electrical stimulation can lead to activation of detrusor inhibitory reflex as well as striated urethral muscles contraction (4). This kind of treatment can cause hypertrophy of muscle fibers, possibly by the recruitment of motor units with faster conduction and alter the expression of myosin isoforms, favoring a conversion to type l muscle fibers (4). An effect of FES at the peripheral level can be modulation of neurotransmitters such as

cholinergic and β-adrenergic system (16). In a study by Ishigooka et al., reduction in norepinephrine content of the rabbit urinary bladder by a combination of yohimbine and electrical stimulation of pelvic floor musculature has been reported. These authors have suggested the reflexive activation of hypogastric nerves following pelvic floor stimulation (17). This finding can describe the effect of FES therapy in patients with bladder overactivity.

Therapeutic effects of FES may be achieved through normalization and balance between cholinergic and beta-adrenergic neurotransmitters (8). The prolonged intravaginal FES restores the normal reflex pattern of detrusor function through reorganization of the neural system innervating the bladder (18).

Results of our present pilot study revealed that transcutaneous FES of striated urethral sphincter decreased daily incontinence score, number of enuresis, and frequency of pad changing in 75% of MMC patients. In addition, significant improvement obtained in the UDS parameters (DLPP, MBC) three months after the treatment. We used this form of stimulation to strengthen the striated urethral muscles and to normalize voiding pattern with activation of afferent fibers of pudendal nerve in the perineal region.

We have yielded improvement in urinary symptoms of children with MMC applying FES in the present study, which was similar to the results of our previous study in MMC children. In our previous study, we used interferential electrical current to decrease urinary incontinence symptoms in MMC children with bladder overactivity: in which 78% of patients gained continence immediately after treatment and 60% of patients remained continent for 6 months or more (15).

To our knowledge, there is no report on the efficacy of FES on urinary symptoms in MMC children. There are several studies investigating therapeutic effects of FES on urinary incontinence among adult female subjects.

Primuse and Kramer reported effects of FES treatment using intravaginal or intra-anal electrodes in 75 patients with complaints of urgency and/or urge incontinence (30 multiple sclerosis and 45 idiopathic patients). In these patients, 59% experienced significant urodynamic and subjective improvement after the treatment and additional 40% of the patients had only subjective improvement of urinary symptoms. Therapeutic effects of electrical stimulation remained for at least 2 years in 64% of patients with idiopathic urinary incontinence while early symptom relapse occurred 2 months after the treatment in multiple sclerosis group (8).

In a study by Hung et al., the effect of FES-biofeedback and pelvic floor muscle exercise on symptoms of women with genuine stress urinary incontinence has been investigated. They have reported that the level of discomfort in daily life, social activity, physical activity, and personal relations due to urinary symptoms had significantly improved especially in the FES-biofeedback group (19).

In a study by Kralj et al., effect of FES on female urinary incontinence has been evaluated. They have reported 50.5% cure, 23.4% improvement of symptoms, and 26.1% treatment failure three months after the treatment (20).

Eskiyurt et al., have compared the effectiveness of two therapeutic method including functional magnetic stimulation (FMS) and functional electrical stimulation (FES) in 22 women with mixed urinary incontinence. Urinary diaries and micturition frequency was more cured and improved in those treated by FES than FMS. However, there was no significant reduction of nocturnal voiding frequency in both groups (21).

There are several limitations in our present study including small sample size, lack of sham-controlled group, and short duration of follow-up. It will be necessary to design future studies to investigate the role of FES therapy in children with myelomeningocele and compare its effect in a sham-controlled design.

CONCLUSIONS

This type of electrical stimulation is an effective and inexpensive therapeutic method for urinary incontinence in children affected by myelomeningocele with no considerable adverse effects and can be used at home. Applying transcutaneous electrodes makes this type of electrical stimulation a less invasive therapeutic method than anal or vaginal electrode and seems to be better tolerated by children.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Wu HY, Baskin LS, Kogan BA: Neurogenic bladder dysfunction due to myelomeningocele: neonatal versus childhood treatment. J Urol. 1997; 157: 2295-7.
2. Nijman RJ: Neurogenic and non-neurogenic bladder dysfunction. Curr Opin Urol. 2001; 11: 577-83.
3. Kajbafzadeh AM, Chubak N: Simultaneous Malone antegrade continent enema and Mitrofanoff principle using the divided appendix: report of a new technique for prevention of stoma complications. J Urol. 2001; 165: 2404-9.
4. Fehrling M, Fall M, Peeker R: Maximal functional electrical stimulation as a single treatment: is it cost-effective? Scand J Urol Nephrol. 2007; 41: 132-7.
5. Malm-Buatsi E, Nepple KG, Boyt MA, Austin JC, Cooper CS: Efficacy of transcutaneous electrical nerve stimulation in children with overactive bladder refractory to pharmacotherapy. Urology. 2007; 70: 980-3.
6. Brubaker L: Electrical stimulation in overactive bladder. Urology. 2000; 55(5A Suppl): 17-23; discussion 31-2.
7. Bower WF, Yeung CK: A review of non-invasive electro neuromodulation as an intervention for non-neurogenic bladder dysfunction in children. Neurourol Urodyn. 2004; 23: 63-7.
8. Primus G, Kramer G: Maximal external electrical stimulation for treatment of neurogenic or non-neurogenic urgency and/or urge incontinence. Neurourol Urodyn. 1996; 15: 187-94.
9. Nevéus T, von Gontard A, Hoebeke P, Hjälmås K, Bauer S, Bower W, et al.: The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol. 2006; 176: 314-24.
10. Schurch B, Stöhrer M, Kramer G, Schmid DM, Gaul G, Hauri D: Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol. 2000; 164: 692-7.
11. Swana HS, Sutherland RS, Baskin L: Prenatal intervention for urinary obstruction and myelomeningocele. Int Braz J Urol. 2004; 30: 40-8.
12. Barbosa LL, Liguori R, Ottoni SL, Barroso U Jr, Ortiz V, Macedo A Jr: Is continent urinary diversion feasible in children under five years of age? Int Braz J Urol. 2009; 35: 459-66.
13. Taskinen S, Fagerholm R, Rintala R: Mini-invasive collagen sling in the treatment of urinary incontinence due to sphincteric incompetence. Int Braz J Urol. 2007; 33: 395-400; discussion 400-6.
14. Caldwell KP: The electrical control of sphincter incompetence. Lancet. 1963; 2: 174-5.
15. Kajbafzadeh AM, Sharifi-Rad L, Baradaran N, Nejat F: Effect of pelvic floor interferential electrostimulation on urodynamic parameters and incontinency of children with myelomeningocele and detrusor overactivity. Urology. 2009; 74: 324-9.
16. Okada N, Igawa Y, Ogawa A, Nishizawa O: Transcutaneous electrical stimulation of thigh muscles in the treatment of detrusor overactivity. Br J Urol. 1998; 81: 560-4.
17. Ishigooka M, Hashimoto T, Sasagawa I, Nakada T: Reduction in norepinephrine content of the rabbit urinary bladder by alpha-2 adrenergic antagonist after electrical pelvic floor stimulation. J Urol. 1994; 151: 774-5.
18. Fall M, Lindström S: Electrical stimulation. A physiologic approach to the treatment of urinary incontinence. Urol Clin North Am. 1991; 18: 393-407.
19. Sung MS, Hong JY, Choi YH, Baik SH, Yoon H: FES-biofeedback versus intensive pelvic floor muscle exercise for the prevention and treatment of genuine stress incontinence. J Korean Med Sci. 2000; 15: 303-8.
20. Kralj B: Conservative treatment of female stress urinary incontinence with functional electrical stimulation. Eur J Obstet Gynecol Reprod Biol. 1999; 85: 53-6.
21. Bölükbas N, Vural M, Karan A, Yalçin O, Eskiyurt N: Effectiveness of functional magnetic versus electrical stimulation in women with urinary incontinence. Eura Medicophys. 2005; 41: 297-301.

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EDITORIAL COMMENT

Children with lower urinary tract congenital anomalies such as bladder exstrophy, myelomeningocele, or posterior urethral valves, can develop complex clinical pictures consisting in high-pressure/low flow and hypertonic low compliant bladders (1). These patients often may need surgical treatment (i.e. cystoplasty) as they often develop resistance to drug treatment.

In children with myelomeningocele, the main aim of treatment is to improve the functionality of diseased bladders by decreasing the intravesical pressures, improving bladder compliance, urinary and fecal continence and patient's quality of life. Patients with a poorly compliant bladder may incur renal damage over time and thus an early effective and conservative management of bladder dysfunction is welcome. Surgical treatment may be effective, but side effects are not negligible: bladder augmentation is usually done with gastrointestinal segments, which can lead to metabolic abnormalities such as acidosis or alkalosis, depending on the segment used, an increased rate of calculi formation, increased mucus production, and enhanced risk of malignant disease (2,3).

Kajbafzadeh and colleagues in this issue of International Brazil Journal of Urology investigated the efficacy of transcutaneous functional electrical stimulation (FES) in a small group of children with myelomeningocele and lower urinary tract dysfunction. Over 12 patients, 9 children reported an improvement on urinary incontinence score, although three children had no improvement. It is interesting to note that the detrusor leak point pressure was significantly improved as well as the maximum bladder capacity. Authors concluded that FES therapy might have positive effects on improvement of voiding symptoms of children with neurogenic urinary incontinence in terms of daily incontinence score and urodynamic parameters.

Every conservative strategy to improve lower urinary dysfunction of children with neurogenic bladder is welcome, but long-term multiparametric (objective and subjective) follow-up remains the challenge for next generation of pediatric and adult urologists.

REFERENCES

1. Snodgrass WT, Adams R: Initial urologic management of myelomeningocele. Urol Clin North Am. 2004; 31: 427-34.
2. McDougal WS: Metabolic complications of urinary intestinal diversion. J Urol. 1992; 147: 1199-208.
3. Soergel TM, Cain MP, Misseri R, Gardner TA, Koch MO, Rink RC: Transitional cell carcinoma of the bladder following augmentation cystoplasty for the neuropathic bladder. J Urol. 2004; 172: 1649-51; discussion 1651-2.

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Effect of Biomolecules from Human Renal Matrix of Calcium Oxalate Monohydrate (CaOx) Stones on In Vitro Calcium Phosphate Crystallization

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ABSTRACT

Purpose: Investigate the activity of high and low molecular weight biomolecules present in the matrix of human calcium oxalate (CaOx) stones not only on the initial mineral phase formation of calcium and phosphate (CaP) but also on its growth and demineralization of the preformed mineral phase.
Materials and Methods: Surgically removed renal stones were analyzed by Fourier Transform Infra Red (FTIR) spectroscopy and only CaOx stones were extracted with 0.05M EGTA, 1 mM PMSF and 1% β-mercaptoethanol. Renal CaOx stone extract was separated into > 10 kDa and < 10 kDa fractions by dialysis. Activity of both the fractions along with whole extract was studied on the three mineral phases of CaP assay system.
Results: It was interesting to observe that both high and low molecular weight biomolecules extracted from human renal matrix of calcium oxalate (CaOx) stones exhibited different roles in the three mineral phases of CaP. Whole extract exhibited inhibitory activity in all the three assay systems; however, mixed (stimulatory and inhibitory) activity was exhibited by the > 10 kDa and < 10 kDa fractions. SDS-PAGE analysis showed bands of 66 kDa, 80 kDa, 42 kDa in whole EGTA extract lane and > 10 kDa fraction lane.
Conclusion: Both high and low molecular weight biomolecules extracted from human renal matrix of calcium oxalate (CaOx) stones have a significant influence on calcium and phosphate (CaP) crystallization.

Key words: *calcium phosphate; calcium oxalate; EGTA; brushite; organic matrix protein*
Int Braz J Urol. 2010; 36: 621-8

INTRODUCTION

Often calcium oxalate stones are mixed with various percentages of apatite or brushite, and some studies have shown that apatite is the principal component of Randall's plaque and the primary nidus at which calcium oxalate stones grow (1,2). Pure apatite and brushite stones are composed of similar chemical components, calcium and phosphate, but the crystalline structure is different. The theoretical ratio of calcium and phosphate in brushite [$CaH(PO_4)\cdot 2H_2O$] is 1.0, and in apatite [$Ca_{10}(PO_4)_6(OH)_2$] is 1.7, though biological apatite often has a ratio less than these (3). A. Randall demonstrated that interstitial crystals located at, or adjacent to, the papillary tip, Randall's plaques, were common in stone formers. He found that these crystals were composed not of calcium oxalate, the most common solid phase found in patients with nephrolithiasis, but of calcium phosphate. He believed that the calcium phosphate crystals formed in the papillary interstitium and then eroded into the urinary space, serving as a heterogeneous nucleation surface for calcium oxalate (4). Romberg et al. have reported that macromolecular modifiers of calcium oxalate

crystallization (5) are also active in the corresponding stages of calcium phosphate crystallization. The heterogeneous nucleation theory also underlines the importance of calcium phosphate crystals in calcium oxalate urolithiasis. All this evidence suggests that there is a close relationship between calcium phosphate and calcium oxalate. Any alteration in calcium phosphate binding protein may lead to the increased deposition of calcium oxalate, by acting as a nidus or calcium oxalate binding protein may influence calcium phosphate crystallization. The aim of the present work was to study the activity of biomolecules present in the organic matrix of calcium oxalate on calcium phosphate crystallization.

MATERIALS AND METHODS

Human renal stones were obtained from the Urology Department of Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. Calcium oxalate stones were confirmed after Fourier Transform Infra Red (FTIR) spectroscopy analysis. All stones were of non-infectious nature. Chemicals were of analytical grade and were used without further purification. Reagents were made with deionized, distilled water.

Extraction of Stones

Surgically removed human renal stones (60 gms) were pooled and extracted for the study. 0.15 M NaCl solution was used for washing the kidney stones to remove the adhered blood and tissue. They were then dried and pulverized with a mortar and pestle. The powder thus obtained was extracted with 0.05M EGTA, 1 mM PMSF and 1% β-mercaptoethanol. The extraction was carried out for 4 days at 4ºC with constant stirring. The suspension was centrifuged for 30 minutes at 10,000g and at 4ºC. The supernatant of EGTA extract was filtered through Amicon ultra centrifugal filter device with a molecular weight cut off 10,000 Daltons at 4ºC and concentrated to a known volume. Whole EGTA extract, greater than and less than 10,000 Dalton fractions were stored at -20ºC for further studies (6).

Protein Assay & SDS-PAGE

The protein concentration of each fraction was measured by the Bradford method (7). For SDS-PAGE each fraction was lyophilized and reconstituted with sample buffer containing β-mercaptoethanol. Samples were heated to 95ºC for 5 min. and were submitted to electrophoresis using 1 mm thick, 12% separating and 4.4% stacking gels with a Mini-Protean III apparatus (Bio-Rad Laboratories). Broad range molecular weight markers (catalog # 161-0317, Bio-Rad) were used as standards. Protein bands were stained with silver using ProteoSilver™ Plus Silver Stain Kit (PROTSIL2, Sigma-Aldrich Corp. Bangalore, India.).

Homogeneous Assay System of Initial Mineral Phase of Calcium Phosphate

To determine the activity of calcium phosphate (CaP) precipitation, homogenous mineralization system was used to study the extent of in vitro mineral phase formation in the absence of any matrix (8). The 5 mL homogenous system consisted of 5 mM $CaCl_2$ and 5 mM KH_2PO_4, Tris buffer (0.1M Tris and 210 mM NaCl [pH 7.4]) and distilled water. After incubating this system at 37^0C, precipitates obtained were centrifuged and the pellets were resuspended in 0.1N HCl (9). The calcium (Ca^{2+}) and phosphate ions (HPO_4^{2-}) concentration in the precipitate represented the extent of precipitation (crystallization) of these ions and the biomolecule(s) will either minimize or maximize the extent of their precipitation. The Ca^{2+} and HPO_4^{2-} ions were estimated by the methods of Trinder (10) and Gomori (11) respectively. Percentage inhibition or stimulation of mineral phase in the presence of kidney stone extract (whole extract, > 10 kDa & < 10 kDa fraction) was calculated as: %age Inhibition = [(C-T)/C] X 100, where T is the concentration of Ca^{2+} or HPO_4^{2-} ion of the precipitate formed in the assay system with the kidney stone extract and C is the concentration of Ca^{2+} or HPO_4^{2-} ion of the precipitate formed in control system which had distilled water (Millipore (India) Pvt. Ltd., Bangalore, India).

Homogeneous Assay System of Growth and Demineralization of Calcium Phosphate Mineral Phase

The growth and demineralization of preformed mineral phase consisting of calcium phosphate required initial precipitates of these minerals as obtained by the initiation of calcium phosphate mineral phase. To study the growth of the preformed mineral phase, the precipitates formed by the above method were resuspended in the same assay system having calcium and phosphate along with the three fractions of kidney stone extract. This assay system was incubated at 37^0C for 30 minutes. Then Ca^{2+} and HPO_4^{2-} ions were estimated and the concentration of these ions represented the growth of precipitation of these ions over the previously formed mineral phase.

For demineralization, the preformed mineral phase was resuspended in the assay system with all the three fractions of kidney stone extract but without further addition of calcium and phosphate ions. This assay system was incubated at 37^0C for 30 minutes. Ca^{2+} and HPO_4^{2-} ions were estimated in supernatant to determine the demineralization of mineral phase by all the three fractions of kidney stone extract.

In case of growth of pre-formed mineral phase, concentration of Ca^{2+} and HPO_4^{2-} ions was deducted from the final concentration of Ca^{2+} and HPO_4^{2-} ions. The percentage inhibition or stimulation caused by different fractions of renal extract was calculated with respect to control system, which had distilled water instead of kidney stone extract. In case of demineralization, the percentage inhibition of Ca^{2+} and HPO_4^{2-} ions demineralized, was calculated in supernatant.

RESULTS

Initial Mineral Phase

The 98.97% of phosphate ion inhibition was exhibited by the whole renal stone extract, 85.9% by > 10 kDa and 92.09% by < 10 kDa fraction on in vitro homogenous assay system of calcium phosphate (Figure-1A). However, whole extract showed maximum 81.64% of calcium ion inhibition. Interestingly both type of activity stimulatory (maximum 25.2%) as well as inhibitory activity (maximum 25.01%) was shown by > 10 kDa fraction. < 10 kDa fraction showed 96.23% of maximum inhibition (Figure-1B).

Growth of Preformed Mineral Phase

In cases where growth of preformed mineral phase percentage inhibition of phosphate ions increased with the increase of whole extract volume, > 10 kDa fraction stimulated the growth of phosphate ions on preformed mineral phase whereas < 10 kDa showed both types of activity (Figure-2A).

Inhibition of calcium ions was shown by whole extract and < 10 kDa fraction on the growth of preformed mineral phase. Stimulation was seen by various volumes of > 10 kDa fraction (Figure-2B).

Demineralization of Preformed Mineral Phase

Release of phosphate ions increased with the increase of volume of different fractions. Maximum amount of phosphate was released with whole extract (Figure-3A). Percentage release of calcium ions were decreased with the increase of different extract volumes. Low volume of whole extract resulted in maximum release of calcium ions (Figure-3B).

Protein Estimation & SDS-PAGE

Protein content of crude (239.5µg/mL) and > 10 kDa (154.8µg/mL) fraction was high. < 10 kDa fraction had less (72.6µg/mL) amount of protein.

SDS-PAGE analysis revealed a large number of bands mainly (66 kDa, 80 kDa, 42 kDa) in whole extract and in > 10 kDa fraction (Figure-4). Faint bands of low molecular weight appeared in < 10 kDa lane (not shown in the image).

COMMENTS

Urolithiasis is known to be an affliction to humankind from ancient eras (12) and is the third

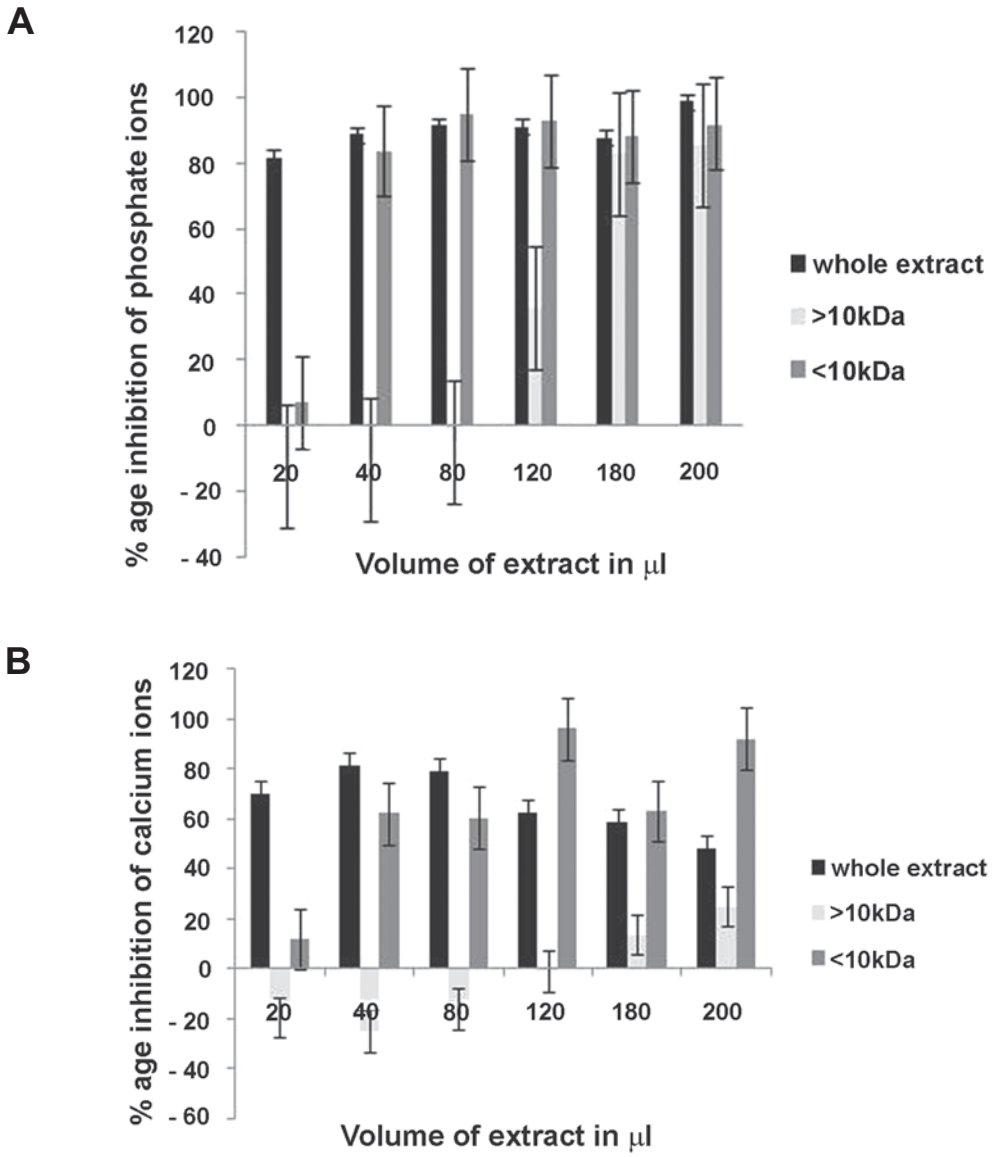

Figure 1 *– Effect of various volumes of renal stone extract(whole extract, > 10kDa, < 10kDa) on initial mineral phase. Percentage inhibition/stimulation of phosphate ions (A) and calcium ions (B) by different renal stone extracts.*

most common cause of urinary tract disease (13). Among all types of kidney stones the frequency of calcium stone is 70-80%, struvite stone 5-10%, uric acid stone 5-10%, and cystine stone 1% (14). Calcium oxalate is the primary component of 70-80% of calcium stones (15-17) with calcium phosphate being the predominant component in the rest of calcium stones. Calcium phosphate kidney stones include apatite (carbapatite or hydroxyapatite (HAP)), brushite (Bru) and octacalcium phosphate (OCP) with the occurrence rate of apatite, 4-10%; Bru, 2-6%; and octacalcium phosphate, less than 1% (14). A recent study has reported that the occurrence of calcium phosphate containing stones has increased over time (18). Calcium phosphate occurs in stones in several different forms: amorphous calcium phosphate (ACP), HAP,

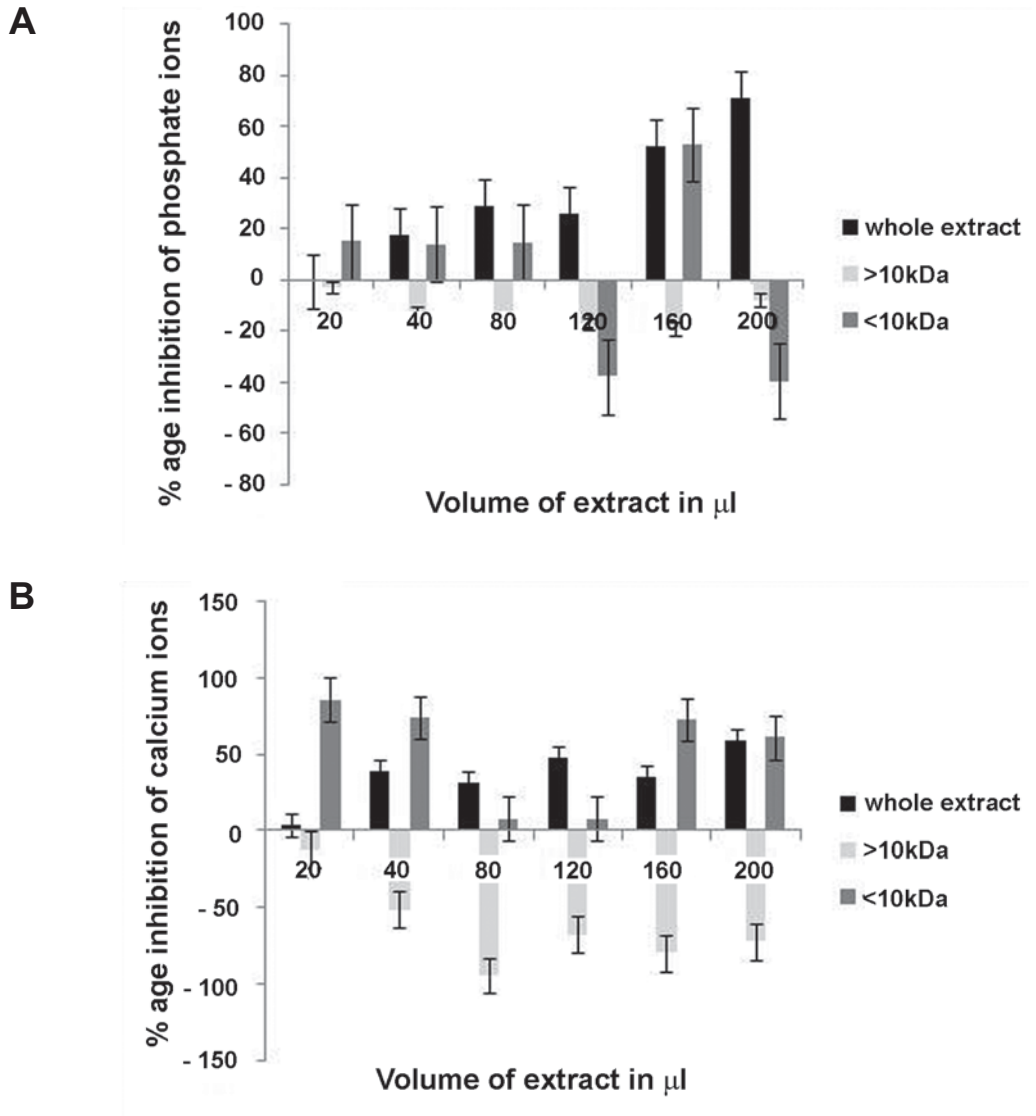

Figure 2 – *Percentage inhibition or stimulation of phosphate ions (A) and calcium ions (B) by different volumes of whole extract, > 10kDa and < 10kDa fractions of renal stone extract on the growth of preformed mineral phase.*

Bru, whitlockite, and carbonate apatite (CarbAp). The first product that precipitates is an ACP, which subsequently is converted to the crystal phases OCP and HAP or occasionally Bru. Hydroxyapatite is the thermodynamically most stable calcium phosphate crystal phase and it is also the major crystal phase in mixed calcium oxalate/calcium phosphate stones. Under certain conditions brushite (Bru; calcium hydrogen phosphate) is formed (19-21).

In this study we determined whether the renal calculi organic matrix biomolecules of calcium oxalate had any functional role in calcium phosphate crystallization. Whole EGTA extract exhibited inhibitory activity in initial and growth mineral phase. Stimulatory and inhibitory activity was shown by > 10 kDa fraction in initial mineral phase. Stimulatory activity was retained in growth mineral phase by this fraction. < 10 kDa had inhibitory activity in initial

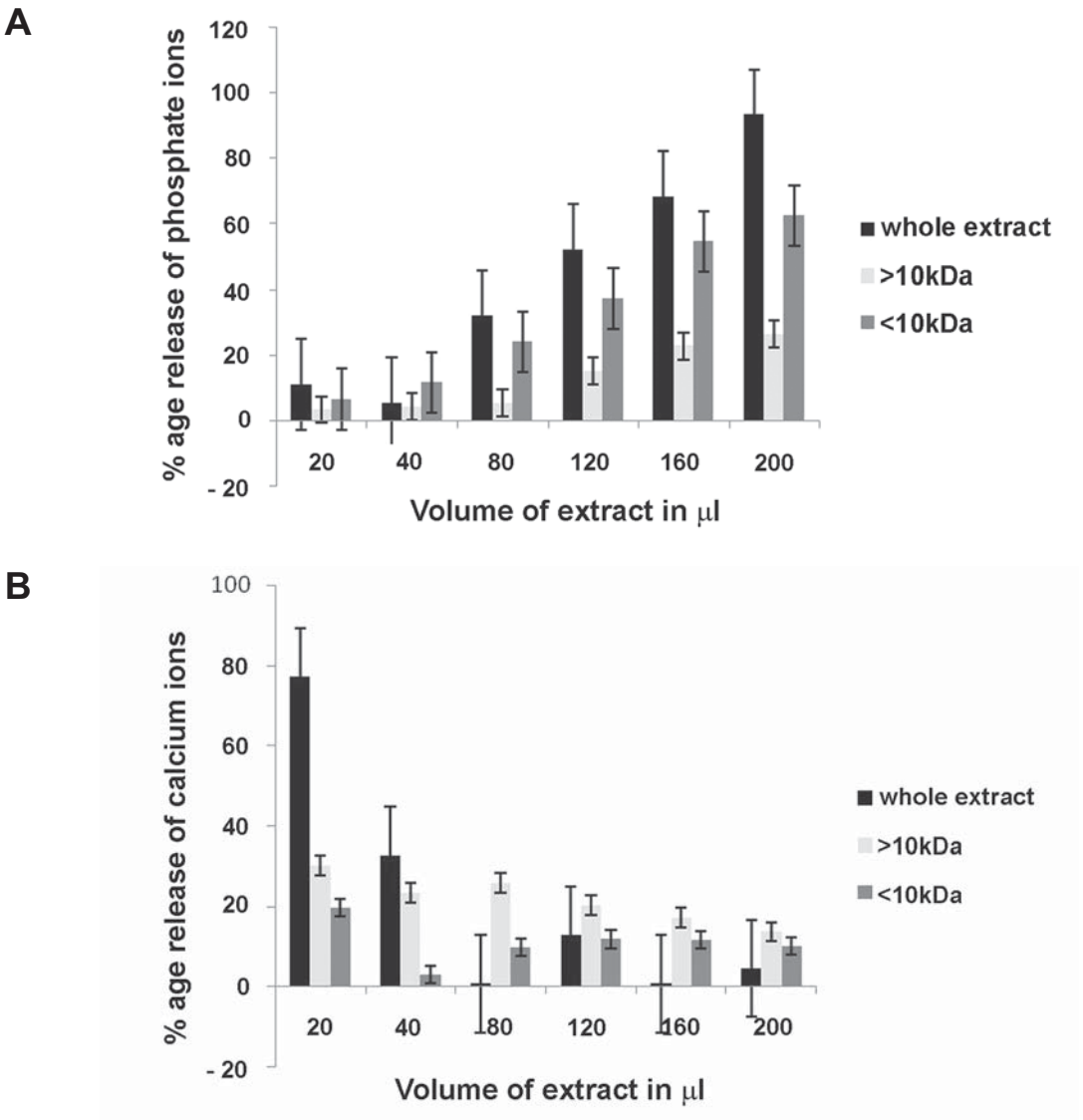

Figure 3 *– Effect of various volumes of renal stone extract (whole extract, > 10kDa, < 10kDa) on demineralization of preformed mineral phase. Percentage of phosphate ions (A) and calcium ions (B) demineralized by different fractions of renal stone extract.*

mineral phase. Both types of activity was shown by < 10 kDa fraction in growth mineral phase.

High percentage of phosphate ion was released with high volume of all the three fractions. However, the opposite trend was observed with calcium ion demineralization. It was found that high percentage of calcium ion was released with low volume of all the three fractions.

Romberg et al. have reported that macromolecular modifiers of calcium oxalate crystallization (4) are also active in the corresponding steps of calcium phosphate crystallization. There is, however, evidence that Mg, citrate, and pyrophosphate are the most important inhibitors of calcium phosphate crystal growth.

There are reports explaining the activity of uric acid binding protein (22) and calcium phosphate binding protein (23) on calcium oxalate crystallization. The predominant proteins found in organic matrices of CaOx crystals induced in the urine of

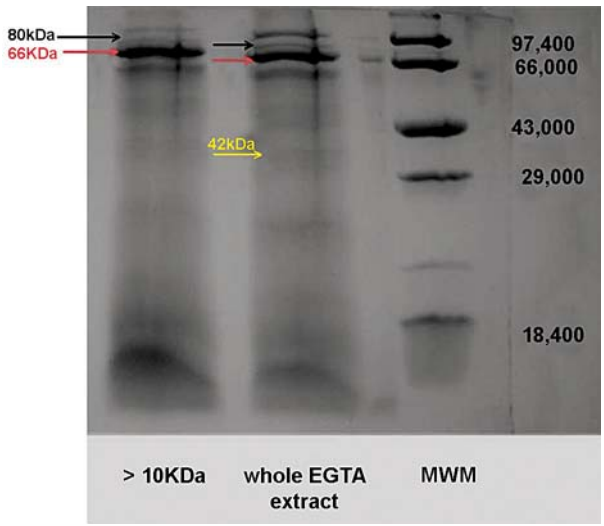

Figure 4 *– SDS-PAGE showing bands in whole EGTA extract and in >10 kDa fraction.*

healthy controls were prothrombin-related proteins followed by albumin and osteopontin. In matrices of CaP crystals, the principal proteins were Tamm-Horsfall protein followed by albumin, prothrombin-related proteins and osteopontin (24). In our study, besides other bands, SDS-PAGE analysis also showed bands of MW ~ 66 kDa, 80 kDa and 42 kDa in whole EGTA extract lane and > 10 kDa fraction lane. Interestingly, their molecular weights are quite close to that of albumin, Tamm-horsfall protein and osteopontin/uropontin respectively. In our laboratory, very recently an anionic protein (MW ~ 42 kDa) with potent inhibitory activity against CaOx crystal growth was purified. It was identified by MALDI-TOF-MS followed by database search on MASCOT server as human phosphate cytidylyltransferase 1, ß. Molecular weight of this novel CaOx crystal growth inhibitor from human renal stone matrix is also the same as that of human phosphate cytidylyltransferase 1, choline, β (25). Osteopontin (OPN) and Tamm-Horsfall protein (THP) are two major urinary macromolecules that exhibit various activities that can influence calcium crystallization in vitro (26,27). OPN is a ubiquitously expressed phosphoglycoprotein that regulates bone biomineralization and ectopic calcification (28,29).

Therefore, our study suggest that both high and low molecular weight biomolecules extracted from human renal matrix of calcium oxalate (CaOx) stones have a significant influence on calcium and phosphate (CaP) crystallization.

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CONFLICT OF INTEREST

None declared.

REFERENCES

1. Evan AP, Lingeman JE, Coe FL, Parks JH, Bledsoe SB, Shao Y, et al.: Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. J Clin Invest. 2003; 111: 607-16.
2. Matlaga BR, Williams JC Jr, Kim SC, Kuo RL, Evan AP, Bledsoe SB, et al.: Endoscopic evidence of calculus attachment to Randall's plaque. J Urol. 2006; 175: 1720-4; discussion 1724.
3. Pramanik R, Asplin JR, Jackson ME, Williams JC Jr: Protein content of human apatite and brushite kidney stones: significant correlation with morphologic measures. Urol Res. 2008; 36: 251-8.
4. Bushinsky DA: Nephrolithiasis: site of the initial solid phase. J Clin Invest. 2003; 111: 602-5.
5. Romberg RW, Werness PG, Riggs BL, Mann KG: Inhibition of hydroxyapatite crystal growth by bone-specific and other calcium-binding proteins. Biochemistry. 1986; 25: 1176-80.
6. Aggarwal S, Tandon CD, Forouzandeh M, Singla SK, Kiran R, Jethi RK: Role of biomolecules from human renal stone matrix on COM crystal growth. Mol Cell Biochem. 2000; 210: 109-19.
7. Bradford MM: A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem. 1976; 72: 248-54.
8. Kabra SG, Kabra V, Banerji P, Jain LK, Bhargava A, Chaturvedi RP: In vitro calculogenesis: methods to

develop concretions of desired chemical composition. Indian J Exp Biol. 1978; 16: 212-7.
9. Bijarnia RK, Kaur T, Singla SK, Tandon C: A novel calcium oxalate crystal growth inhibitory protein from the seeds of Dolichos biflorus (L.). Protein J. 2009; 28: 161-8.
10. Trinder P: Colorimetric microdetermination of calcium in serum. Analyst. 1960; 85: 889-94.
11. Gomori HD: A modification of colorimetric phosphorus determination for use with photoelectric colorimeter. J Lab Clin Med. 1941; 27: 955-960.
12. Miyaoka R, Monga M: Use of traditional Chinese medicine in the management of urinary stone disease. Int Braz J Urol. 2009; 35: 396-405.
13. Amaro CR, Goldberg J, Amaro JL, Padovani CR: Metabolic assessment in patients with urinary lithiasis. Int Braz J Urol. 2005; 31: 29-33.
14. Morton AR, Wooltorton E: Nephrology in practice: a new series. CMAJ. 2002; 166: 195.
15. Herring LC: Observations on the analysis of ten thousand urinary calculi. J Urol. 1962; 88: 545-62.
16. Mandel NS, Mandel GS: Urinary tract stone disease in the United States veteran population. II. Geographical analysis of variations in composition. J Urol. 1989; 142: 1516-21.
17. Tefekli A, Esen T, Ziylan O, Erol B, Armagan A, Ander H, et al.: Metabolic risk factors in pediatric and adult calcium oxalate urinary stone formers: is there any difference? Urol Int. 2003; 70: 273-7.
18. Mandel N, Mandel I, Fryjoff K, Rejniak T, Mandel G: Conversion of calcium oxalate to calcium phosphate with recurrent stone episodes. J Urol. 2003; 169: 2026-9.
19. Leusmann DB, Niggemann H, Roth S, von Ahlen H: Recurrence rates and severity of urinary calculi. Scand J Urol Nephrol. 1995; 29: 279-83.
20. Györy AZ, Ashby R: Calcium salt urolithiasis. Review of theory for diagnosis and management. Clin Nephrol. 1999; 51: 197-208.
21. Hesse A, Heimbach D: Causes of phosphate stone formation and the importance of metaphylaxis by urinary acidification: a review. World J Urol. 1999; 17: 308-15.
22. Kalaiselvi P, Udayapriya KL, Selvam R: Uric acid-binding proteins in calcium oxalate stone formers and their effect on calcium oxalate crystallization. BJU Int. 1999; 83: 919-23.
23. Nishio S, Hatanaka M, Takeda H, Aoki K, Iseda T, Iwata H, et al.: Calcium phosphate crystal-associated proteins: alpha-2-HS-glycoprotein, prothrombin fragment 1 and osteopontin. Int J Urol. 2001; 8: S58-62.
24. Atmani F, Khan SR: Quantification of proteins extracted from calcium oxalate and calcium phosphate crystals induced in vitro in the urine of healthy controls and stone-forming patients. Urol Int. 2002; 68: 54-9.
25. Priyadarshini, Singh SK, Tandon C: Mass spectrometric identification of human phosphate cytidylyltransferase 1 as a novel calcium oxalate crystal growth inhibitor purified from human renal stone matrix. Clin Chim Acta. 2009; 408: 34-8.
26. Devuyst O, Dahan K, Pirson Y: Tamm-Horsfall protein or uromodulin: new ideas about an old molecule. Nephrol Dial Transplant. 2005; 20: 1290-4.
27. Kumar V, Lieske JC: Protein regulation of intrarenal crystallization. Curr Opin Nephrol Hypertens. 2006; 15: 374-80.
28. Giachelli CM, Steitz S: Osteopontin: a versatile regulator of inflammation and biomineralization. Matrix Biol. 2000; 19: 615-22.
29. Mo L, Liaw L, Evan AP, Sommer AJ, Lieske JC, Wu XR: Renal calcinosis and stone formation in mice lacking osteopontin, Tamm-Horsfall protein, or both. Am J Physiol Renal Physiol. 2007; 293: F1935-43.

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STONE DISEASE

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Endoscopic management of completely excluded calices: a single institution experience

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Background and Purpose: Excluded calices refer to a single calix or multiple calices that are completely isolated from the collecting system. The etiology is a result of infection, malignancy, or inflammation that is secondary to endoscopic renal surgery. We report our experience with the endoscopic management of excluded calices.
Patients and Methods: We retrospectively reviewed the data for our patients with a diagnosis of excluded calices. Patients were treated with various endoscopic techniques, all necessitating the formation of a neoinfundibulum. Patients were evaluated for symptomatic and radiographic evidence of resolution.
Results: Eight patients were found to have excluded calices. Seven patients had a history of urolithiasis and previous endoscopic renal surgery. One patient had undergone a laparoscopic partial nephrectomy with a post-operative urinary fistula. Six of eight patients were treated with a percutaneous approach followed by laser incision, balloon dilatation, or nephroureteral stent placement. Two objective failures occurred. One patient received re-treatment and has not demonstrated persistence or recurrence since the second procedure. No complications occurred as a result of endoscopic management.
Conclusion: Excluded calices commonly result from inflammation from previous renal surgery. Goals of management include relief of obstruction, management of stones, and regaining continuity with the remaining collecting system. Successful treatment with endoscopic management involves creation of a neoinfundibulum and placement of a temporary ureteral stent.

Editorial Comment

The excluded calyx is a rare phenomenon - at this specialized tertiary referral center for complex stones, only two cases were seen per year. More commonly one might anticipate the findings of a localized hydrocalyx on CT scan would represent an infundibular stenosis. Retrograde pyelography is essential to differentiate the two entities, as a short infundibular stenosis could be addressed ureteroscopically.

The authors report the use of fluoroscopy to identify the hydrocalyx, yet it is unclear how this was employed if the excluded calyx could not be opacified with retrograde contrast. The authors do not report how they selected patients for a percutaneous versus ureteroscopic approach to creation of the neo-infundibulutomy. One might propose that anterior hydrocalyces may be best suited to a retrograde attempt rather than performing an initial percutaneous puncture into an adjacent posterior calyx and then through the renal pelvis. It also may be that ureteroscopic guidance during percutaneous access might facilitate identification and puncture of the hydrocalyx.

The authors do not report the criteria used for stenting with one versus two ureteral stents, or the size of stent used. In addition scheduled radiographic imaging to document absence of recurrence and/or failure was not reported.

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Factors affecting the success of ureteroscopy in management of ureteral stone diseases in children

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Purpose: We retrospectively investigated the factors that affect the success of rigid ureteroscopy in the pediatric population for the management of pediatric ureteral stones.
Patients and Methods: We present a retrospective review of 61 consecutive pediatric patients who underwent 66 rigid ureteroscopy procedures for ureteral stone management. The effects of sex, age, stone diameter, stone localization, and degree of associated ureterohydronephrosis (UHN) on the success of ureteroscopy were evaluated.
Results: The mean age of the patients was 8.1 years (range 6 mos-16 yrs). The average stone diameter was 8.22 mm (range 4-20 mm). In 56 cases (84.8%), all of the stones were extracted. In five (7.6%) cases, clinically significant residual fragments were detected and extracted by second-look ureteroscopy. In five cases (7.6%), the operations ended in failure. The final stone clearance rate after ureteroscopic stone treatment was higher in lower ureteral stones then in middle and upper ureteral stones; thus, the difference was statistically significant ($P = 0.011$). Also, there is a significant negative correlation between stone size and success rate ($P = 0.007$). The final stone clearance rate after ureteroscopic stone treatment was higher in patients with no and mild UHN than in patients with moderate and severe UHN, but the difference was statistically insignificant ($P = 0.118$). Statistical analyses revealed no significant relationship between success rates with regard to the sex and age of the patients ($P = 0.643$ for sex, $P = 0.390$ for age).
Conclusion: The stone localization and stone size are the factors that affect the success of the procedure.

Editorial Comment

The study spans a time period of 11 years - such that an average of 6 patients were treated per year. In addition, six urologists participated in this study - such that on average each urologist performed only one procedure. This raises the question - should collaboration between pediatric and adult urologist be encouraged for endoscopic stone procedures - maintaining facility in instrumentation and technique for advanced ureteroscopic procedures may require a higher case volume.

The success rate of 85% is excellent. The addition of flexible ureteroscopy, holmium laser lithotripsy, small caliber semirigid (4.5/6F) ureteroscopes and 1.5F stone baskets could further advance ureteroscopy in the pediatric population. One would anticipate that the addition of these instrumentations would minimize the impact of stone location as a predictor of success.

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ENDOUROLOGY & LAPAROSCOPY

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Cryoablation vs. radiofrequency ablation for small renal masses

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Rationale and Objectives: Cancer of the kidney is the third most common cancer of the urinary tract, and renal cell carcinoma is the most lethal of all genitourinary tumors. The incidental discovery of renal cell carcinoma has increased with increased use of cross-sectional imaging. Concomitantly, minimally invasive ablative technologies, including image-guided cryoablation, radiofrequency ablation, and others, have evolved as therapeutic options for small renal masses.
Materials and Methods: Between 2006 and 2009, 111 patients (age range, 31-91 years; mean age, 70 years) underwent percutaneous computed tomography-guided thermal ablation for suspected renal cell carcinoma at two major academic centers. Outcomes data were retrospectively collected and analyzed to compare recurrence rates for patients undergoing radiofrequency ablation (n = 41) versus cryoablation (n = 70).
Results: There were four cases of suspicious enhancement on follow-up computed tomography or magnetic resonance imaging in each group, with cumulative imaging recurrence rates of 11% and 7% for radiofrequency ablation and cryoablation, respectively. Log rank test analysis revealed no significant difference between rates of imaging recurrence between the two groups (P = .6044).
Conclusions: These results suggest that the use of cryoablative technology will result in similar outcomes compared with radiofrequency ablation.

Editorial Comment

Renal masses have been increased in incidence in the last 50 years due to advances in imaging technology. From large incisions excisions and surgical procedures we have evolved as specialty to minimally invasive organ sparing surgery.

Ablative technology has emerged as alternative treatment modality to manage and treat small renal masses.

This paper describes the percutaneous ablative cryo and RFA outcomes for the treatment of renal masses.

As described by other centers the outcomes are consistent with the findings. The main concern is the participation of Urologists when these procedures are occurring and also the follow-up and management of complications when urologists are not involved from the beginning. The patient will benefit from any procedures when the diseases are treated by the specialists or group of specialists that understand the illness rather than application of technology.

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Histopathological predictors of renal function decrease after laparoscopic radical nephrectomy

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Purpose: Radical nephrectomy is inevitably associated with a variable renal function decrease. We assessed the association of histopathological parameters in nonneoplastic renal parenchyma with the renal function decrease after radical nephrectomy.
Materials and Methods: We evaluated 32 male and 17 female patients with a mean age of 55.9 years who underwent laparoscopic radical nephrectomy. Using the Cockcroft-Gault formula we calculated the estimated glomerular filtration rate preoperatively and at last follow-up at a mean of 19.7 months. The study end point was the percent change in the estimated glomerular filtration rate from baseline, defined as (absolute change/baseline) × 100. Three histological features in the nonneoplastic parenchyma were assessed by a renal pathologist, including global glomerulosclerosis, arteriosclerosis and interstitial fibrosis/tubular atrophy. For glomerulosclerosis assessment the percent of affected glomeruli was determined. Arteriosclerosis or the extent of arterial luminal occlusion was graded into 4 groups, including 1-0% to 5%, 2-6% to 25%, 3-26% to 50% and 4-greater than 50%. However, due to small patient numbers groups 1 and 2, and 3 and 4 were condensed, and AS was statistically evaluated as 0% to 25% or greater than 25%. Interstitial fibrosis/tubular atrophy was evaluated as absent/present.
Results: The mean estimated glomerular filtration rate decreased 31% from 122 to 85 mL/minute/1.73 m(2) after surgery ($p < 0.0001$). The percent change in the estimated glomerular filtration rate was associated with glomerulosclerosis extent ($p = 0.034$). For each 10% increase in glomerulosclerosis the estimated glomerular filtration rate decreased by 9% from baseline. The extent of arteriosclerosis or the presence of interstitial fibrosis/tubular atrophy did not correlate with the estimated glomerular filtration rate decrease.
Conclusions: Glomerulosclerosis severity in nonneoplastic parenchyma can predict the rate of renal function decrease after radical nephrectomy. This histopathological parameter should be assessed in all tumor nephrectomy specimens, given that preserving renal function is important for quality of life and clinical outcome in patients with renal cancer.

Editorial Comment

The authors should be congratulated for the pioneer work that demonstrates the relationship between extends of glomerulosclerosis associated with decrease in postoperative eGFR in patients post radical nephrectomy. For every 10% increase in GS there was a 9% decrease in eGFR.

This study supports the idea of nephron-sparing surgery for the treatment of renal masses. The clinical long-term implications should be weighted when discussing with patients all management options, so we can optimize therapy with minimal decrease of quality of life.

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IMAGING

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Tumor characteristics of urothelial carcinoma on multidetector computerized tomography urography

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Purpose: We investigated the relationship between tumor characteristics of urothelial carcinoma and detectability on multidetector computerized tomography urography.
Materials and Methods: We retrospectively reviewed all adult consecutive patients with hematuria who underwent multidetector computerized tomography urography during a 23-month period at our hospital. Patients with a final diagnosis of urothelial carcinoma verified by histological examination of surgical specimens were included in the study. The presence and location of urothelial carcinomas on multidetector computerized tomography urography without knowledge of final diagnosis were recorded. Tumor characteristics (location, size, histological classification and stage) were recorded based mainly on histological findings. The association between tumor characteristics and urothelial carcinoma detectability on multidetector computerized tomography urography was analyzed.
Results: A total of 70 patients who underwent multidetector computerized tomography urography had 87 verified urothelial carcinomas. Of these carcinomas 6 (6.9%) were undetectable by multidetector computerized tomography urography, including 5 ureteral and 1 bladder urothelial carcinoma. Size of detectable and nondetectable tumors on multidetector computerized tomography urography differed significantly (3.05 +/- 1.79 vs 0.65 +/- 0.99 cm, respectively, p = 0.001). Tumor location (p = 0.009), tumor size 1 cm or larger (p = 0.003) and noncarcinoma in situ tumors (p = 0.001) were significantly associated with multidetector computerized tomography urography detectability. Conversely organ confined disease had no association with multidetector computerized tomography urography detectability. Multivariate analyses showed that noncarcinoma in situ tumor was a significant predictor of multidetector computerized tomography urography detectability (p = 0.001).
Conclusions: Multidetector computerized tomography urography is useful for detecting nearly all urothelial carcinomas in adults with hematuria. Careful assessment by multidetector computerized tomography urography is needed to detect small (less than 1 cm) or ureteral urothelial carcinomas. It remains a challenge to detect carcinoma in situ tumors by multidetector computerized tomography urography. Thus, negative results of urothelial carcinomas on multidetector computerized tomography urography do not exclude the presence of carcinoma in situ tumors.

Editorial Comment

Multidetector CT-urography (MDCT-urography) has been shown to be an effective single comprehensive examination in the evaluation of patients with hematuria or with risk for the development of urothelial malignancies. In this manuscript a total of 201 adults underwent MDCT- urography as imaging investigation of hematuria. Interesting point to consider is number of patients in whom this test was important to determine the etiology of hematuria. Seventy patients (34%), had urothelial cancer and other 88(43%) had other urological abnormalities responsible for the hematuria. Specifically in patients with urothelial cancer, 85.7% presented with gross hematuria and 14.3% presented with microscopic hematuria. These results emphasize the value of MDCT-urography as a tool for investigation of either gross or microscopic hematuria particularly in older patients. In this series 7 % of tumors were undetectable by MDCT- urography, including 5 ureteral and 1 bladder

urothelial carcinoma. There are a variety of reasons for false-negative diagnoses of ureteral and bladder cancer during MDCT- urography. Early-enhanced thin-section MDCT of a full bladder with urine can decrease the number of false negatives bladder studies. This "bladder -wall phase ", obtained 60 seconds after contrast injection has superior accuracy for detection of small lesions in comparison with the excretory phase alone (bladder fully distended by opacified urine), as used by the authors. However small flat tumors that do not appear as filling defects and carcinoma in situ tumors, are almost impossible to be detected by MDCT-urography. For this reason, although not a perfect test, cystocopy remains the reference standard procedure in the investigation of hematuria.

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Prostate cancer managed with active surveillance: role of anatomic MR imaging and MR spectroscopic imaging

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Purpose: To determine the role that magnetic resonance (MR) imaging and MR spectroscopic imaging findings obtained at the time of diagnosis play in the progression of disease in patients whose prostate cancer is being managed with active surveillance and to compare the role of these findings with the role of transrectal ultrasonography (US) findings.
Materials and Methods: The institutional review board approved this HIPAA-compliant retrospective study, and informed consent was obtained from all patients whose records were to be entered into the research database. All patients who had prostate cancer managed with active surveillance and who had undergone both MR imaging and MR spectroscopic imaging of the prostate and transrectal US at time of diagnosis were identified. Two urologists blinded to the clinical outcome in these patients independently reviewed and dichotomized the MR imaging report and the MR spectroscopic imaging report as normal or suggestive of malignancy. One experienced urologist performed all US examinations that were then dichotomized similarly. Uni- and multivariate (with use of standard clinical variables) Cox models were fitted to assess time to cancer progression, defined as Gleason score upgrading, prostate-specific antigen velocity of more than 0.75 (microg x L(-1))/y, or initiation of treatment more than 6 months after diagnosis.
Results: The final cohort included 114 patients with a median follow-up of 59 months. Patients with a lesion that was suggestive of cancer at MR imaging had a greater risk of the Gleason score being upgraded at subsequent biopsy (hazard ratio, 4.0; 95% confidence interval: 1.1, 14.9) than did patients without such a lesion. Neither MR spectroscopic imaging nor transrectal US could be used to predict cancer progression.
Conclusion: Abnormal prostate MR imaging results suggestive of cancer may confer an increased risk of Gleason score upgrade at subsequent biopsy. Although expensive, prostate MR imaging may help in counseling potential candidates about active surveillance.

Editorial Comment

The incorporation of combined MRI/MRSI and multiparametric MRI in the active surveillance program is still investigational. The possible application of these techniques is based on the fact that volumetric and metabolic data correlates with tumor aggressiveness (1).

Recently study has been shown that combined MR imaging and MR spectroscopic imaging findings and Ki-67 (a proliferation marker), pAkt (a serine-threonine kinase), and androgen receptor values correlated with each other and with clinically insignificant and significant prostate cancers (2). In another study, MRI/MRSI models performed better than the clinical models for predicting the probability of insignificant prostate cancer (3). In the study by Fradet et al., patients presenting a hypointense focal area on T2-weighted image, suspicious for cancer at the time of diagnosis, had a greater risk of the Gleason score being upgraded at subsequent biopsy than did patients without such a lesion. Interesting is that MR spectroscopic imaging which is more specific for tumor characterization, than conventional T2-weighted images, was not useful to predict cancer progression. We agree with the authors that after appropriate validation, the MRI and MRI/MRSI models might help in counseling patients who are considering choosing deferred therapy.

References

1. Zakian KL, Sircar K, Hricak H, Chen HN, Shukla-Dave A, Eberhardt S, et al.: Correlation of proton MR spectroscopic imaging with gleason score based on step-section pathologic analysis after radical prostatectomy. Radiology. 2005; 234: 804-14.
2. Shukla-Dave A, Hricak H, Ishill NM, Moskowitz CS, Drobnjak M, Reuter VE, et al.: Correlation of MR imaging and MR spectroscopic imaging findings with Ki-67, phospho-Akt, and androgen receptor expression in prostate cancer. Radiology. 2009; 250: 803-12.
3. Shukla-Dave A, Hricak H, Kattan MW, Pucar D, Kuroiwa K, Chen HN, et al.: The utility of magnetic resonance imaging and spectroscopy for predicting insignificant prostate cancer: an initial analysis. BJU Int. 2007; 99: 786-93.

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PATHOLOGY

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Optimizing performance and interpretation of prostate biopsy: a critical analysis of the literature

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Context: The number and location of biopsy cores and the interpretation of prostate biopsy in different clinical settings remain the subjects of continuing debate.
Objective: Our aim was to review the current evidence regarding the performance and interpretation of initial, repeat, and saturation prostatic biopsy.

Evidence Acquisition: A comprehensive Medline search was performed using the Medical Subject Heading search terms prostate biopsy, prostate cancer, detection, transrectal ultrasound (TRUS), nomogram, and diagnosis. Results were restricted to the English language, with preference given to those published within the last 3 yr.
Evidence Synthesis: At initial biopsy, a minimum of 10 but not > 18 systematic cores are recommended, with 14-18 cores in glands ≥ 50cm(3). Biopsies should be directed laterally, and transition zone (TZ) cores are not recommended in the initial biopsy setting. Further biopsy sets, either as an extended repeat or as a saturation biopsy (≥ 20 cores) including the TZ, are warranted in young and fit men with a persistent suspicion of prostate cancer. An immediate repeat biopsy is not indicated for prior high-grade prostatic intraepithelial neoplasia diagnosis given an adequate extended initial biopsy. Conversely, biopsies with atypical glands that are suspicious but not diagnostic of cancer should be repeated within 3-6 mo. Overall recommendations for further biopsy sets (a third set or more) cannot be made. Transrectal ultrasound-guided systematic biopsies represent the standard-of-care method of prostate sampling. However, transperineal biopsies are an up-to-standard alternative.
Conclusions: The optimal prostatic biopsy regimen should be based on the individualized clinical setting of the patient and should follow the minimum standard requirements reported in this paper.

Editorial Comment

The article is from a selected group of uropathologists giving several recommendations for optimizing performance and interpretation of prostate biopsies. The highlights are:

a) At initial biopsy, a minimum of 10 but not more than 18 systematic cores;
b) In cases of glands iqual or larger than 50 cm3, 14-18 cores;
c) Transition zone cores are not recommended in the initial biopsy setting;
d) An immediate repeat biopsy is not indicated for prior high-grade intraepithelial neoplasia (HGPIN) given an adequate extended initial biopsy;
e) Biopsies with atypical glands that are suspicious but not diagnostic of cancer should be repeated within 3-6 months.

Note that the authors do not use the term ASAP but "suspicious but not diagnostic of cancer". The term ASAP for "atypical small acinar proliferation" was coined by Iczkowski et al. in 1997 (1), however is not recommended by uropathologists. In a consensus meeting in 2004 sponsored by the World Health Organization (2), the committee members recommended designating ASAP as either suspicious or highly suspicious for cancer. The reasons for this include the equation by some urologists of the term ASAP with HGPIN, and because all of the atypical foci are not always "small" acinar but may include glands with a larger diameter (such as pseudohyperplastic pattern of cancer or adenocarcinoma with ductal features).

References

1. Iczkowski KA, MacLennan GT, Bostwick DG: Atypical small acinar proliferation suspicious for malignancy in prostate needle biopsies: clinical significance in 33 cases. Am J Surg Pathol. 1997; 21: 1489-95.
2. Amin M, Boccon-Gibod L, Egevad L, Epstein JI, Humphrey PA, Mikuz G, Newling D, Nilsson S, Sakr W, Srigley JR, Wheeler TM, Montironi R: Prognostic and predictive factors and reporting of prostate carcinoma in prostate needle biopsy specimens. Scand J Urol Nephrol Suppl. 2005; 216: 20-33.

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International Society of Urological Pathology (ISUP) Consensus Conference on Handling and Staging of Radical Prostatectomy Specimens. Working group 2: T2 substaging and prostate cancer volume

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Abstract: The 2009 International Society of Urological Pathology consensus conference in Boston made recommendations regarding the standardization of pathology reporting of radical prostatectomy specimens. Issues relating to the substaging of pT2 prostate cancers according to the TNM 2002/2010 system, reporting of tumor size/volume and zonal location of prostate cancers were coordinated by working group 2. A survey circulated before the consensus conference demonstrated that 74% of the 157 participants considered pT2 substaging of prostate cancer to be of clinical and/or academic relevance. The survey also revealed a considerable variation in the frequency of reporting of pT2b substage prostate cancer, which was likely a consequence of the variable methodologies used to distinguish pT2a from pT2b tumors. Overview of the literature indicates that current pT2 substaging criteria lack clinical relevance and the majority (65.5%) of conference attendees wished to discontinue pT2 substaging. Therefore, the consensus was that reporting of pT2 substages should, at present, be optional. Several studies have shown that prostate cancer volume is significantly correlated with other clinicopathological features, including Gleason score and extraprostatic extension of tumor; however, most studies fail to demonstrate this to have prognostic significance on multivariate analysis. Consensus was reached with regard to the reporting of some quantitative measure of the volume of tumor in a prostatectomy specimen, without prescribing a specific methodology. Incorporation of the zonal and/or anterior location of the dominant/index tumor in the pathology report was accepted by most participants, but a formal definition of the identifying features of the dominant/index tumor remained undecided.

Editorial Comment

The clinical staging of prostate cancer reflects the detection methods employed. Substaging of clinical stage T2 prostate carcinoma is based on the extent of the abnormality palpated during a digital rectal examination. In the 2009 TNM system for prostate cancer the clinical and pathological substaging of T2 cancers are classified into 3 groups: T2a (tumor involves one-half of one lobe or less), T2b (tumor involves more than one-half of one lobe, but not both lobes), and T2c (tumor involves both lobes) (1).

Pathologic staging tries to maintain symmetry with clinical staging, allowing a direct comparison of both. However, in contrast to clinical substaging of T2 prostate cancers, is controversial whether pathologic T2 substaging conveys prognostic information.

During the consensus conference sponsored by the International Society of Urological Pathology (ISUP) on handling and staging of radical prostatectomy specimens held in Boston during the 98th meeting of the United States and Canadian Academy of Pathology (USCAP), 65.5% of the attendants answered that the current pathologic T2 substaging system should not be used. Answering to another question, 63.4% favored to be reduced to two categories based on studies showing that pathological T2b tumor does not exist (2,3).

The lack of symmetry between clinical and pathological T2 staging may be apparently explained in part by the fact that clinical criteria used in assessing stage indirectly estimate the chance of understaging and in this way they seem to stratify the heterogeneous group of clinical stage T2 patients (4). The multifocality seen in 83-87% of prostate cancers (5,6) is another cause for the absence of symmetry between clinical and pathological T2 substaging. Prostate cancer may be extensive on one lobe (index tumor) and only insignificant

on the other side. Should this case be considered pT2c? In this particular example what should be a minimum extent for a case to be considered bilateral? During the consensus conference there was no consensus regarding definition of index tumor, and the minimum size for a second tumor to be considered for the whole case to be classified as pT2c.

Overview of the literature indicates that current pathological T2 substaging criteria lack clinical relevance and the majority of conference attendees wished to discontinue pT2 substaging. Therefore, the consensus was that reporting of pathological T2 substages should, at present, be optional.

References

1. International Union Against Cancer (UICC). TNM Classification of malignant tumours, 7th ed, Sobin LH, Gospodarowicz M, Wittekind Ch (eds). Geneva:Wiley-Blackwell, 2009, pp. 243-8.
2. Eichelberger LE, Cheng L: Does pT2b prostate carcinoma exist? Critical appraisal of the 2002 TNM classification of prostate carcinoma. Cancer. 2004; 100: 2573-6.
3. Quintal MM, Magna LA, Guimaraes MS, Ruano T, Ferreira U, Billis A: Prostate cancer pathologic stage pT2b (2002 TNM staging system): does it exist? Int Braz J Urol. 2006; 32: 43-7.
4. van der Kwast TH: Substaging pathologically organ confined (pT2) prostate cancer: an exercise in futility? Eur Urol. 2006; 49: 209-11.
5. Arora R, Koch MO, Eble JN, Ulbright TM, Li L, Cheng L: Heterogeneity of Gleason grade in multifocal adenocarcinoma of the prostate. Cancer. 2004; 100: 2362-6.
6. Wise AM, Stamey TA, McNeal JE, Clayton JL: Morphologic and clinical significance of multifocal prostate cancers in radical prostatectomy specimens. Urology. 2002; 60: 264-9.

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RECONSTRUCTIVE UROLOGY

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The use of uroflowmetry to diagnose recurrent stricture after urethral reconstructive surgery

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J Urol. 2010; 184: 1386-90

Purpose: The ability of uroflowmetry to diagnose recurrent stricture disease after urethroplasty has not been fully investigated.

Materials and Methods: Our routine post-urethroplasty monitoring includes retrograde urethrogram and voiding cystourethrogram at 3 and 12 months, in addition to uroflowmetry at 3-month intervals for a year. All uroflowmetry data, including maximum flow rate, voided volume and voiding curve shape, as well as retrograde urethrogram/voiding cystourethrogram and voiding symptom data are stored in a prospectively maintained urethroplasty database that was analyzed for patients with postoperative retrograde urethrogram/voiding cystourethrogram and satisfactory uroflowmetry in the same period. Uroflowmetry data points and urinary symptoms

were compared with corresponding findings on retrograde urethrogram/voiding cystourethrogram to determine the ability of uroflowmetry to predict recurrence.
Results: A total of 278 men (68%) met study inclusion criteria, of whom 63 (23%) had recurrent stricture. Using a maximum flow rate of less than 10 mL per second resulted in only 54% test sensitivity to predict recurrence. The highest sensitivity and negative predictive value (each 99%) were achieved when all men with symptoms and/or obstructed flow curves were evaluated. Symptoms alone had a high specificity (87%), sensitivity (88%) and negative predictive value (95%).
Conclusions: Uroflowmetry is an adequate test to screen for postoperative stricture recurrence but only when the voiding curve and urinary symptoms are also evaluated. The flow rate alone does not appear to be a reliable tool to evaluate stricture recurrence.

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A simplified protocol for evaluating and monitoring urethral stricture patients minimizes cost without compromising patient outcome

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Trop Doct. 2010; 40: 134-7

Abstract: Uroflowmetry, urethrocystoscopy and urethrography are either not readily available or the cost is prohibitive for many patients in low-resource countries. This paper examines the use of clinical history in post-urethroplasty follow-up. We retrospectively reviewed the outcome of 54 post-urethroplasty patients. Pre-operative diagnostic work-up included simple blood tests and a retrograde urethrography, and postoperatively we did not perform any immediate diagnostic work-up. Follow-up of these patients was done through mobile phone calls and personal contacts. Eighty-nine per cent of our patients reported acceptable voiding over a mean follow-up period of 48.4 months - 79.6% were followed using mobile phone contact. In the majority of the urethral strictures cases, diagnostic work up can be kept to a minimum, thereby reducing cost. Follow-up can be done via phone calls and personal contact in many African countries where compliance is frequently less than encouraging. The spread of mobile phone networks across the continent has been remarkable.

Editorial Comment

The study by Erickson et al. seeks to arrive at a non-invasive means of predicting urethral stricture recurrence after urethroplasty. Uroflowmetry is attractive in that it is an objective test. The authors state that maximum urinary flow rate is not by itself a very good predictor of failure but that the combination of maximum flow rate, voiding pattern and urinary obstructive symptoms is predictive. Indeed, the combination of these three factors was the most predictive of a man having a recurrence (PPV 90%); yet this combination misses half the strictures (sensitivity 51%). This low sensitivity means few physicians would be inclined to forgo more invasive testing in any man. Although it was the goal of the authors to find a predictive tool, what would be more helpful to the patient would be a screening tool. A good screening tool helps a portion of the population avoid advanced confirmatory testing, while still preserving high sensitivity. With the latter goal in mind, a high threshold for maximum urinary flow rate (< 20 cc/sec) has excellent sensitivity (92%) and NPV (96%), meaning that it captures 92% of strictures and only misses 4%. While PPV is low (48%) this is acceptable as a screening tool - it just means that a little more than half of men who undergo RUG/VCUG will have no recurrent stricture. At the same time, more than half of the population in this study could avoid a RUG/VCUG because their flow rates were over 20 cc/sec - this is the proper role of a screening tool.

The goal of identifying a useful screening tool for urethral stricture recurrence is echoed in the second article, by Okorie et al. They describe using mobile phones to survey urinary symptoms after urethral stricture treatment. Although the symptoms reported over the telephone were not validated objectively, the concept of telephone follow-up is important, especially in areas of the world where travel to a referral center is difficult. Others have previously shown that home measurement of timed urinary flow correlates well with office-measured maximum urinary flow rate (1). If we were able to validate a means of screening patients over the telephone with timed urinary flow rates with or without telephone-administered validated questionnaires we could spare many patients the travel to a referral center for continued follow-up.

Reference

1. Bloom DA, Foster WD, McLeod DG, Mittemeyer BT, Stutzman RE: Cost-effective uroflowmetry in men. J Urol. 1985; 133: 421-4.

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UROLOGICAL ONCOLOGY

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Should bladder cuff excision remain the standard of care at nephroureterectomy in patients with urothelial carcinoma of the renal pelvis? A population-based study

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Background: A large, multi-institutional, tertiary care center study suggested no benefit from bladder cuff excision (BCE) at nephroureterectomy in patients with upper tract urothelial carcinoma (UC).
Objective: We tested and quantified the prognostic impact of BCE at nephroureterectomy on cancer-specific mortality (CSM) in a large population-based cohort of patients with UC of the renal pelvis.
Design, Setting, And Participants: A cohort of 4210 patients with UC of the renal pelvis were treated with nephroureterectomy with (NUC) or without (NU) a BCE between 1988 and 2006 within 17 Surveillance, Epidemiology, and End Results registries.
Measurements: Cumulative incidence plots and competing risks regression models compared CSM after either NUC or NU. Covariates consisted of pathologic T and N stages, grade, age, year of surgery, gender, and race.
Results and Limitations: Respectively, 2492 (59.2%) and 1718 (40.8%) patients underwent a nephroureterectomy with or without BCE. In univariable and multivariable analyses, BCE omission increased CSM rates in patients with pT3N0/x, pT4N0/x, and pT(any)N1-3 UC of the renal pelvis. For example, in patients with pT3N0/x disease, holding all other variables constant, BCE omission increased CSM in a 1.25-fold fashion

(p=0.04). Similarly, in patients with pT4N0/x disease, BCE omission resulted in a 1.45-fold increase (p=0.02). The main limitation of our study is the lack of data on disease recurrence.
Conclusions: Nephroureterectomy with BCE remains the standard of care in the treatment of UC of the renal pelvis and should invariably be performed in patients with locally advanced disease. Conversely, patients with pT1 and pT2 disease could be considered for NU without compromising CSM. However, recurrence data are needed to fully confirm the validity of this option.

Editorial Comment

Bladder cuff excision was regarded standard in all upper urinary tract urothelial tumors. Recently, however, this standard was challenged by reports that did not show any benefit from this procedure. Therefore, this large international, multi-institutional analysis from Canada, Italy and Germany including more than 4200 patients with urothelial cancer of the renal pelvis is very helpful in re-establishing the standard of care for this patient group.
Two important observations were made. First, in patients with positive lymph nodes, and in those with >pT2 tumors of the renal pelvis, cancer-specific mortality was significantly higher if bladder cuff excision (BCE) was omitted. Second, no survival benefit was seen in the group with smaller (pT1-2), node-negative tumors. Therefore, BCE may be omitted in select patients of this group.
A drawback of the study to my opinion was the lack of inclusion of ureteral cancers and I would hope that the authors will perform another analysis for this important subgroup, too. Still, these data re-establish the standard and strongly support routine BCE in cases with urothelial renal pelvis tumors.

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Prevention and management of complications following radical cystectomy for bladder cancer

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Context: This review focuses on the prevention and management of complications following radical cystectomy (RC) for bladder cancer (BCa). OBJECTIVE: We review the current literature and perform an analysis of the frequency, treatment, and prevention of complications related to RC for BCa.
Evidence Acquisition: A Medline search was conducted to identify original articles, reviews, and editorials addressing the relationship between RC and short- and long-term complications. Series examined were published within the past decade. Large series reported on multiple occasions (Lee [1], Meyer [2], and Chang and Cookson [3]) with the same cohorts are recorded only once. Quality of life (QoL) and sexual function were excluded.
Evidence Synthesis: The literature regarding prophylaxis, prevention, and treatment of complications of RC in general is retrospective, not standardised. In general, it is of poor quality when it comes to evidence and is thus difficult to synthesise.

Conclusions: Progress has been made in reducing mortality and preventing complications of RC. Postoperative morbidity remains high, partly because of the complexity of the procedures. The issues of surgical volume and standardised prospective reporting of RC morbidity to create evidence-based guidelines are essential for further reducing morbidity and improving patients' QoL.

Editorial Comment

Radical cystectomy (RC) is the treatment of choice for muscle-invasive bladder cancer. RC is a major procedure with an inherent rate of complications and morbidity. This collaborative multi-institutional international review of the literature on prevention and management of complication is recommended reading not only for surgeons involved in such operations but also for urologists in training. Many aspects are covered in detail and reflect the large experience of the authors and their institutions, e.g. fast-track surgery, bowel preparation, perioperative and postoperative complications. Recommendations for prevention and treatment of typical situations are given such as blood loss, urinary extravasation, pneumonia, ileus, lymphocele, metabolic disorders. In summary, it evolves that radical cystectomy is a procedure for experienced urologists only which should be performed in high-volume centers. Many factors before, during and after the operation have to be considered to provide good outcomes for our patients.

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NEUROLOGY & FEMALE UROLOGY

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Prevalence and characteristics of sexual hookups among first-semester female college students

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J Sex Marital Ther. 2010; 36: 346-59

First-semester female college students (N = 118) completed surveys to estimate the prevalence of sexual hookups and event-level assessments to clarify the behavioral characteristics of their most recent hookup. Hookups involving oral, vaginal, or anal sex were reported by 51% before college, 36% during their first semester, and 60% by the end of their first semester. Event-level analyses revealed that hookups were more likely to involve friends (47%) or acquaintances (23%) rather than strangers (14%); alcohol use (median = 3 drinks) preceded 64% of hookups. Condoms were used during 69% of vaginal sex hookups.

Editorial Comment

This article allows the reader to veritably gaze through the proverbial looking glass at the behavior of young female students just beginning their college career. The article states in its first paragraph that one of its goals is to describe what exactly "a hookup" is and how common are these hookups. The authors state that the use of the word hookup is not relegated only to oral or vaginal sex. In fact, they only describe 27% of the

interactions as being truly sex. It seems that even when the brief interaction only includes sexual fondling or kissing, the interaction is felt to be classified as a hookup. Disconcerting for those hopelessly in love with one special person is that friends and acquaintances compromise 70% of the hookups and even strangers (14%) had a higher degree of hooking up than did ex-boyfriends (12%). Of specific interest to the urologist is the notation that condom use was never used for oral sex during these hookups and surprisingly in only 69% of those interactions involving vaginal sex. This statistic is of particular value to remember when examining a young female patient with the potential presentation of the first occurrence of genital herpes or paroxysmal voiding symptoms. The article is well worth the read especially with regards to the discussion and comparison of the characteristics of the casual affair versus the romantic relationship.

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Adjustable continence therapy for severe intrinsic sphincter deficiency and recurrent female stress urinary incontinence: long-term experience

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J Urol. 2010; 184: 1017-21

Purpose: Adjustable continence therapy (ACT) was developed to treat female stress urinary incontinence resulting from intrinsic sphincter deficiency by increasing urethral resistance. We evaluated the implantation procedure and assessed patient outcomes at our center.
Materials and Methods: The adjustable continence device consists of 2 silicone balloons on either side of the proximal urethra under the bladder neck, each attached to a titanium port buried in the labia to allow postoperative titration. Urodynamic assessment was done in 57 female patients in whom previous pelvic surgery had failed. Pad use and an incontinence quality of life questionnaire were evaluated before ACT implantation, postoperatively at 1,3,6 and 12 months, and annually thereafter. Patients recorded the overall impression and percent of improvement postoperatively based on the Patient Global Impression Index and a visual analog scale.
Results: Mean follow-up was 72 months (range 12 to 84). At 6-year follow-up in 29 patients mean pad use improved from 5.6 daily at baseline to 0.41 and intrinsic sphincter deficiency improved from 27.2 to 78.6 ($p < 0.001$). As measured on the visual analog scale, 68% of patients considered themselves dry. On the Patient Global Impression Index questionnaire 64% were very much improved, 23% were much improved and 13% were only minimally improved or unchanged. No patients considered themselves worse after the procedure. Complications necessitating device removal developed in 21.1% of patients.
Conclusions: Relative ease of insertion and the ability to tailor this therapy to individual needs makes this an attractive option for the challenging treatment for recurrent stress urinary incontinence due to intrinsic sphincter deficiency.

Editorial Comment

The authors review their experience with an anti-incontinence device comprised of two silicone balloons which is placed transvaginally and allows for postoperative titration to optimize long-term results. The authors

were able to achieve a self reported dry rate in 68% of their patients with a mean follow-up of 72 months. No patient felt that the procedure made them worse.

When reading this article, many will remember the previous anti-incontinence device termed genitourinary spheroidal membranes which were placed approximately 20 years ago (1). The advantage of this contemporary device is the potential for less migration and the ability to postoperatively titrate. In the past, the genitourinary spheroidal membrane effect could be enhanced by placing more membranes spheres paraurethrally; consequently, on occasion there was some dislodgement with proximal migration of the device(s) into the retropubic space. This adjustable continence device is placed and first allowed to form a pseudo capsule prior to beginning the process of balloon adjustment to address the incontinence. This method seems to have limited the complication of dislodgement and optimized the results in this challenging population of patients with very low Valsalva leak point pressures (< 60 cm water). The device certainly looks appealing and very competitive with injectable therapy but only time will provide the answer whether it will achieve a high level of popularity.

Reference

1. Darson MF, Malizia AA, Barrett DM: Periurethral injection of the genitourinary spheroidal membrane. J Endourol. 1996; 10: 283-6.

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PEDIATRIC UROLOGY

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Value of ultrasound in evaluation of infants with first urinary tract infection

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J Urol. 2010; 183: 1984-8

Purpose: We evaluated the role of ultrasound in diagnosing and treating infants with a first urinary tract infection with a focus on important structural abnormalities.
Materials and Methods: In a setting of limited prenatal ultrasound screening this population based, prospective, 3-year study included 161 male and 129 female infants. Ultrasound and dimercapto-succinic acid scintigraphy were performed as initial investigations and voiding cystourethrography was conducted within 2 months.
Results: Ultrasound revealed dilatation in 15% of patients and increased kidney length in 28%. Sensitivity for detecting scintigraphic abnormality was 48%. Renal length was significantly correlated to inflammatory parameters, including scintigraphic abnormalities. Important structural abnormalities were detected in 40 cases, with 30 on ultrasound, while 10 of 27 cases of dilating reflux (mostly grade III) were missed. Outside the study there were 28 additional cases of structural abnormality, of which 15 were detected prenatally.
Conclusions: Ultrasound detected most structural abnormalities except grade III reflux. Since it is noninvasive, ultrasound has a place in the evaluation of infants with urinary tract infection, especially in the absence of prenatal

ultrasound during late pregnancy. Kidney length in infants with acute infection correlated with inflammatory parameters, and the clinical importance of this finding needs to be studied further.

Editorial Comment

This is a population-based, prospective study looking at all patients younger than one year of age who presented with a urinary tract infection to a single institution over 3 years. They were able to get complete data on 290 patients, all of whom underwent DMSA scan and ultrasonography acutely and then a VCUG within two months of diagnosis. Structural abnormalities were detected in 40 patients. Ultrasound was able to detect abnormalities in all but 10 of these patients. These 10 patients had "dilating" vesicoureteral reflux. 12 of the 40 patients went on to require surgery, but only 6 of those procedures were for reflux. Other important abnormalities detected included UPJ obstruction, UVJ obstruction and ureterocele.

As we continue to evaluate the pros and cons of a top down versus bottom up approach to reflux, this study highlights the continued value of ultrasonography for pediatric patients. Some have questioned the usefulness of ultrasonography for evaluation of children with a urinary tract infection. The fact that ultrasonography is readily available, non-invasive, and does not require radiation exposure will likely ensure that this imaging modality will not be left to the wayside regardless of which approach one chooses.

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Management of abnormal postvoid residual urine in children with dysfunctional voiding

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Urology. 2010; 75: 1472-5

Objectives: To evaluate the effect of biofeedback therapy on the residual urine volume in children with dysfunctional voiding.
Methods: This prospective study was conducted in children with dysfunctional voiding associated with abnormal postvoid residual urine (PVR) from June 2002 to 2007. The children were divided randomly into 2 groups. Group 1 was treated with standard urotherapy combined with biofeedback therapy and group 2 was treated with only standard urotherapy. The outcomes of uroflow-electromyography pattern, urinary tract infection (UTI), and PVR were recorded before and at the end of sixth month of treatment.
Results: A total of 94 patients were enrolled in this study. Groups 1 and 2 consisted of 62 and 32 patients, respectively. The voiding pattern became normal in 80.6% (50/62) and 56.2% (18/32) of patients in groups 1 and 2, respectively. The PVR resolved in 40 of 62 (64.5%) patients in group 1 and in 11 of 32 (34.4%) children in group 2. Before the treatment, UTI was noted in 22.5% of patients (14/62) in group 1 and 21.8% of patients (7/32) in group 2. After the treatment, UTI was observed in 3.2% of patients (2/62) and in 9.3% (3/32) of patients in groups 1 and 2, respectively. Although both treatment modalities changed the voiding pattern, rate of febrile UTI, and PVR positively, these outcomes were better in a combination group.
Conclusions: The combination of standard urotherapy with the biofeedback therapy improved the results significantly.

Editorial Comment

This is a prospective study looking at the efficacy of standard behavioral therapy compared to behavioral therapy plus biofeedback training. The authors enrolled 94 patients in the study, all of whom had a staccato voiding pattern on uroflow consistent with dysfunctional voiding. The authors not only looked at postvoid residuals but also examined the prevalence of urinary tract infection and flow rate at the beginning of the study and after six months of treatment. There were no significant differences in the demographics of the patient populations. Improvement was noted in both groups of patients at the end of the study; however, the biofeedback group had significantly better outcomes in terms of the prevalence of infections, elimination of postvoid residual and improvement in flow rate.

While there is no question that we can improve outcomes in children with standard behavioral therapy alone, this study adds to the growing data demonstrating the improved efficacy of combining this with biofeedback therapy. It would be nice to have some follow-up data to examine the durability of treatment in these patients beyond six months.

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Video

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Laparoscopic Extended Lymphadenectomy for Bladder and Prostate Cancer

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ABSTRACT

Purpose: Extended lymphadenectomy in bladder and prostate cancer represents an important step of the surgical treatment of these tumors. Some urological referral centers have been using the laparoscopic approach for these cases. The aim of this video is to demonstrate the surgical technique of laparoscopic extended lymphadenectomy for bladder and prostate cancer.
Case 1: Patient with transitional cell carcinoma of the bladder invading the muscular layer underwent laparoscopic extended lymphadenectomy up to the aortic bifurcation. Total operative time was 100 minutes and intraoperative bleeding was 100cc. Thirteen nodes were retrieved with no neoplasic involvement.
Case 2: Patient with prostate cancer clinical stage T2 was submitted to laparoscopic extended lymphadenectomy with dissection of the internal iliac artery and its branches. Operative time was 55 minutes and intraoperative bleeding was 100cc. Eleven nodes were retrieved with no neoplasic involvement.
Conclusion: Extended lympadenectomy in bladder and prostate cancer is a challenging procedure that can be performed by using the laparoscopic approach following the oncologic concepts.

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Available at: www.brazjurol.com.br/videos/september_october_2010/Branco_648_649video.htm

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EDITORIAL COMMENT

This video is yet another demonstration of the excellent lymph node dissection that is possible through a laparoscopic approach. It is interesting that we are returning to this technique which was one of the earliest applications for laparoscopy in urology when used to stage prostate cancer. As we enter an era when an increasing amount of urologic malignancies will be performed using a laparoscopic or robotic approach, videos such as this which demonstrate the anatomy and skill set required are mandatory. The author's should be congratulated for the efforts at doing a thorough, oncologically sound procedure without any compromise. When performed in this manner, the lymph node dissection may be performed as well, if not better, than by using an open approach. Although at this time, the laparoscopic and robotic assisted laparoscopic approaches may take longer, they may be performed safely with comparable node counts and resection margins as compared to open (Richard et al). We should all be watching closely to the continued development of this evolving technique.

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